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EDITORIALS

The Arterial Muscle Fiber

A Proposed New Approach to the Source of Essential Hypertension

PREVIOUS studies[1] dealt with past efforts to elucidate the still moot problem of the cause of essential hypertension. Several coherent reasons were then stated, pointing to the smooth arteriolar muscle fiber as the probable genetic source of essential hypertension. From this point of view, it seemed desirable to suggest investigating arteriolar smooth muscle tissue with the aid of the electron microscope.

It is deemed worth while studying arteriolar muscle tissue in search of cytologic findings in cases of essential hypertension which are absent in others. Such comparative study might possibly show a relationship between structural differences of arteriolar muscle tissue and commensurate functional differences in terms of peripheral resistance to the flow of blood. It is reasonable to suggest this task because the arteriolar muscle fiber, in spite of its dominant role in controlling arterial tension, has been, so far, practically ignored.

Significance of Changes in Arteriolar Smooth Muscle: A current publication[3] from a most authoritative source does refer to the smooth muscle of the arteriole as "perhaps the least understood, least studied, and most unappreciated." However, it is not cytologic, structural, but chemical, electrolytic interest which moves those authors to call the arteriolar smooth muscle elements "the chief targets for future research." Even so, it is good to note, at last, some serious concern with not only the various kinds of impulses to which the arteriolar muscle reacts but also "the intensity of response" to such impulses by the smooth muscle itself. It is perhaps a promising omen when distinguished students of essential hypertension begin lending much weight to "the intrinsic tone of arteriolar smooth muscle."

Nearly a quarter of a century ago this writer[2] deemed it cogent to search the arteriolar muscle for the primary guilt in the pathogenesis of essential hypertension. The reader may review the manifold evidence and reasons which were then, and since then, considered.[1] They not only implicate the arteriolar muscle but also suggest "the possibility of a common constitutional background behind the tonus of the arteriolar musculature and the tonus of other supportive tissues in the same organism." It seemed compelling to postulate essential hypertension as the manifestation of an inherited constitution bestowing upon the individual "a certain strength of tonus of the mesenchymatous derivatives, including the smooth arteriolar musculature."

The main question which emerges from such thoughts is: Can any structural stigma be detected in arteriolar smooth muscle cells to which essential hypertension may be attributable?

Although not in connection with the problem of hypertension, the significance of intracellular

elements has long been debated. As part of the general problem of the role of genes, muscle fibrils have been found to harbor genetically molded cytoplasmic particles of certain structural, functionally decisive variability.[4] In other words, the function of muscle fibrils has been traced to such cytoplasmic particles, whose varying quality is responsible for corresponding functional differences of muscle fibrils.

Most illuminating are the electron microscopic studies of the sarcosomes in the myocardial and other muscle fibers. These studies[5] have clearly thrown new light upon the relationship between ultramicroscopic structure and function of muscle fibers.

In England, in a wholly unrelated field of research,[6] the electron microscope has recently disclosed variations in muscle fibers which raised in the minds of those workers, too, the fundamental question: How do these variations influence the responsiveness of the muscle fibers to extraneous effects and age?

To be sure, blood pressure does not depend on the state of the arterial wall alone. It is also a function of various other forces which jointly govern the peripheral resistance to the flow of blood. Certainly, the blood pressure must change with each unopposed alteration of any one of those forces at one or another homeostatic level. However, no such alteration has yet been proved to be the primary cause of essential hypertension.

Regardless of the complexity of the self-regulatory mechanism of arterial tension, about one fact there can be no reasonable doubt: The muscle coat of the arterial tree is the structural unit which receives and executes the orders for a certain state of vasoconstriction, irrespective of their origin or nature, humoral, endocrine, neurogenic or otherwise. The arteriolar muscular coat may be called the *executive organ* of arterial tension.[1] It is equally compelling to conclude that the degree of responsiveness inherent in the vascular muscle fiber must perforce determine the measure of effectiveness of the manifold homeostatic mechanisms reaching the arteriolar muscular coat.

Anyone prone to call this reasoning speculative may question his judgment after a good look at the balance sheet of the past: Over a few decades, an enormous bulk of generally creditable contributions to the study of the pathogenesis of essential hypertension has grown at a staggering price in work and money. It still faces the consensus about our enduring ignorance.[7–9]

Proposed New Approach to the Study of the Arteriolar Muscle Fiber: Without repeating all data in this matter which have been dealt with fully in former publications,[1,2] it may be said, in summary: The proposed new approach is clearly pertinent and based on scientific premises. Investigating the arteriolar muscle fiber with the aid of the electron microscope may help answering the old query: Where lies the source of that kind of arterial hypertension which, to the best of our knowledge, is associated with no pre-existing disease and for which no primary cause is known, save a hereditary, i.e., genetic, predisposition?

It is hoped that the investigation proposed here may be undertaken by many qualified workers who hardly need any advice for a plan of procedure. Nor is the present writer competent in the technologic area of this undertaking. Suffice it to mention only a few points upon which general concurrence may be expected apart from studying the cellular structure of the arteriolar muscle fiber:

(1) Careful and exhaustive examination should precede labeling any case as "essential" hypertension. Under no circumstances should anyone be included in this category without reliable screening.[10]

(2) The material, i.e., arterioles, should be obtained at autopsy, from biopsies (deliberate or incidental), and surgically removed tissues.

(3) The caliber of the arteriole and the thickness of its muscular coat, not of the entire wall, should be recorded in each instance and taken into consideration.

(4) The material should be classified according to age, body build, sex, race, and family history reflecting upon the constitutional, i.e., genetic, background of the individual.

(5) The team should include an histologist or pathologist as well as an internist who would have available to them an electron microscope together with the technical help of an experienced electron microscopist.

(6) Whenever possible, children of normal parents and children of hypertensive parents with

a positive cold pressor test should be included in this study, for comparison with one another.

(7) Experimentally, animals rendered hypertensive by the induction of renal ischemia should have their arteriolar muscle fibers examined before and after the experimental interference. Also, since the giraffe may normally have a blood pressure of 280–345/150–195, examination of its arteriolar muscle fibers would be very desirable.

MARCUS BACKER, M.D., F.A.C.C.
Department of Medicine
St. Vincent's Hospital
Bridgeport, Connecticut

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The Pharmacologic Limitations of Diuretics

IN THE logical selection of a drug for therapeutic use, there must be some reasonable connection between a pharmacodynamic action and a particular dysfunction against which it is to be applied. In the organization of a plan for the fullest as well as safest exploitation of the potentialities of the drug, the association must be made precisely between the effects of the drug in abnormal and changing situations as well as in the normal circumstance. With such an attitude toward the problems of the selection of a drug and the best means of using it, information regarding the pathologic physiology of the condition to be treated as well as the precise effects of the drug in the normal and in disease is of the first importance. It would be well to examine diuretics from this point of view.

THE NATURE OF DIURESIS

Diuretics are commonly conceived as drugs which stimulate renal activity, and the kidney is commonly conceived as an excretory organ. The term "diuretic" has, therefore, strong implications of an action which stimulates the excretory function of the kidney. Such a misconception has, I believe, led to many of the difficulties which have been encountered with the use of diuretics. Perhaps the most important aspect of this misconception is to consider that the kidney has only one important function, that of excretion. The kidney has another function, one which, in many ways, is far more complex and certainly equally vital—the defense of electrolyte, water, and acid-base homeostasis.

Effects of Diuretics on Renal Excretory Function: It is important to identify the effects of drugs on an organ with some precision, especially when the organ has more than one function, for a drug may affect one and not others, or affect each differently. The excretory function of the kidney serves to eliminate endogenous metabolites as well as foreign or exogenous materials and the products of their biotransformation. No diuretic significantly increases the excretion of endogenous metabolites by a direct action. With the single exception of bromide, no diuretic significantly increases the excretion of foreign materials or their end products by a direct

action, and since the exception can be explained on another basis it is not really an exception to the rule. Even in the instance of the xanthine diuretics, which are supposed by some, but not by all, to increase the rate of glomerular filtration, no one claims that this action provides significant increase in renal clearance. It is possible to make a categoric statement therefore that, as matters stand, there are no diuretics available which stimulate the excretory function of the kidney.

Effect of Diuretics on Electrolytes, Water, and Acid-Base Homeostasis: The remaining general function of the kidney, the defense of electrolyte, water, and acid-base homeostasis is a vital, extensive, and complex one. It is this function that all the presently available diuretics influence. Even the instance of bromide poisoning, in which the rate of excretion of bromide can be markedly accelerated by some diuretics, rests on the fact that the kidney and the diuretic tend to treat the high blood bromide level as a form of electrolyte disturbance. What is even more interesting in relation to the popular conception of a diuretic as a renal stimulant is that the only action which diuretics exert on the kidney is not stimulation at all, it is depression of some aspects of tubular resorption—blockade of renal mechanisms involved in maintaining normal electrolyte, water and acid-base relationships.

Effect of Diuretics on Tubular Function: It might be well to review the particular functions of the renal tubule which are depressed by the diuretics. In general, diuretics depress the rate of resorption by the renal tubule of anions and cations of the glomerular filtrate. By so doing, that is, by preventing their resorption, they in fact increase the rate of their elimination. This they may do relatively selectively by depressing particular devices of the transport system of the renal tubule, presumably either through an osmotic or enzymatic action. Only one of the enzymes involved in such processes, carbonic anhydrase, has thus far been identified with certainty. As is well known, this one is depressed by Diamox. There is considerable speculation about the others. There is reason to believe that the mercurial diuretics inhibit some sulfhydryl-containing enzyme but this is just about as far as its identification has proceeded. In the case of other potent diuretics, the mode of action is even more speculative. Whatever the precise mechanism of this action, the diuretics currently in use can be best described as drugs which increase the rate of elimination of electrolyte in the urine.

Effect on Electrolyte Excretion: By virtue of interference with the transport of anions and cations across the renal tubule the rate of excretion of certain of them can be increased with some degree of specificity by particular diuretics. Any of these actions which eventually results in an increased rate of excretion of the fixed base, sodium, will thereby increase water elimination to the degree that the excreted sodium frees bound water. Depending on the particular anions eliminated with the sodium, the urine becomes more alkaline or more acid, blood chloride rises or falls, blood bicarbonate rises or falls. Insofar as there is an effect which increases cation elimination, blood sodium may fall. In addition, because the action on cation resorption is never entirely specific for sodium, potassium excretion may be increased to a lesser or greater degree and blood and tissue potassium content will fall accordingly. Depending on the nature as well as the extent of any of these effects, blood pH may also rise or fall.

From such a point of view it can be said that we have available now diuretics which, in the normal electrolyte milieu at least, can be counted upon to increase the elimination of sodium, chloride, and bicarbonate relatively selectively, and to a more limited degree there are some diuretics which have a greater tendency than others to increase the rate of potassium excretion. In all instances, however, the water diuresis is secondary to the natriuresis. On the other hand, by the very nature of their action electrolyte disturbance is inherent in their use and the danger of serious disturbance of electrolyte homeostasis is implicit in their poorly designed application.

Statements on the specificity of the effect on electrolyte elimination of one or another diuretic can by no means be made categorically; yet, when they are burdened with all the qualifications that are necessary to take into account the variable influence of circumstance they become

unwieldy. The fact is, that while in the normal electrolyte situation the action of a particular diuretic can be well described and is predictable, its relative specificity changes with alterations in the electrolyte status.

The simplest example is to be found in the case of the exchange resins. When the sodium content of the intestine is high and the potassium low, the acid exchange resins remove a great deal of sodium and relatively little potassium, but when the reverse is the case, as it is usually when a low-sodium diet is used, sodium removal is likely to be minimal and potassium removal relatively greater. Diuretics which act on the kidney directly are also influenced by the electrolyte milieu in which they operate; mercurial and xanthine diuretics are less effective saluretic agents when blood chloride levels are low; carbonic anhydrase inhibitors remove relatively less sodium when the blood chloride level rises and bicarbonate level falls. Since the nature of the diuresis induced by these drugs bears a relationship to the situation in which they operate and, since the situation is subject to change, both spontaneously and as the result of the treatment itself, the character of electrolyte diuresis may also change during the course of treatment with the same drug.

Thus, it may develop that a diuretic which has a highly desirable effect on electrolyte status at one stage of treatment becomes a different type of ion diuretic at another stage of the treatment and thereby undesirable. It is this fact which may be correlated with the clinical observation that it is the so-called resistant case in which most of the difficulties develop with the use of these drugs. It is the consequence of the failure to recognize that resistance may involve an exceptional electrolyte status, and that since in resistant cases, the usual type of diuresis does not develop, the possibility for an abnormal effect on electrolyte through pursuing the use of the drug in relatively larger or more frequent dosage is greater than in the usual clinical situation. An atypical situation for its use may well lead to an atypical action on the part of a particular diuretic.

The Basis for a Decision to Apply Diuresis

A logical choice of a diuretic, therefore, implies a correlation between a disturbance in electrolyte homeostasis and the capacity for the diuretic to correct it. The term "disturbance in homeostasis" is a broad one with a multiplicity of implications, yet the area in which these drugs are useful is exceedingly narrow, and they are of great practical value only because of the fact that a single use applies to an exceedingly large number of patients with the same condition, cardiac edema. In edemas other than cardiac, diuretics are of little use and at best uncertain. The other conditions in which diuretics as such are consistently useful are few, and those instances are of relatively uncommon conditions.

The reason for the limited applicability of drugs which affect so fundamental a process as electrolyte disturbance lies in the fact that diuretics act to increase the rate of electrolyte loss rather than to replenish lost electrolyte, whereas electrolyte loss rather than excess is the basis of the more common forms of electrolyte disturbances which are recognized as such.

In edema, the situation of dramatic effectiveness in the one form, the cardiac, and the usual futile application in the others, has led to considerable speculation on the essential differences between them. The evidence is clear enough that in cardiac edema, for one reason or another, the kidney resorbs sodium more effectively than it normally does. Here a drug which blockades sodium resorption is obviously desirable and this, of course, is what the diuretics now in use do so effectively. In other edemas, nutritional, obstructive, inflammatory, hepatic, while there may be some sodium retention, other factors not susceptible to the action of diuretics to blockade tubular resorption apparently play an important role and only insofar as an increase in renal excretion of sodium can help can diuretics help the situation.

Since the circumstances in which this may apply are irregularly present, diuretics are of little practical use in noncardiac edemas. Where they have been applied with more than the usually predictable lack of success as, for example, has been reported after chlorothiazide, there has also been a high incidence of hypopotassemia or other untoward effects. Insofar as some of the edemas may represent disturbances in aldosterone activity it would seem to me to be more logical to seek a new diuretic

for these edemas with an action which antagonizes aldosterone. For this reason it seems to be that, as matters stand and with the diuretics now available, only cardiac edema provides the proper setting for their predictable use. For disturbances in electrolyte balance, water balance, and renal activity, other drugs with facets of action not now available will have to be developed, drugs whose actions apply to the disturbance in homeostasis and not merely to the symptom, edema.

The Design for Diuresis

Only therapy which takes into account (1) the nature of the fluid or electrolyte to be removed; (2) the ease with which it can be done in the particular case with the specific agents available; (3) the need for speed in its removal; and (4) the setting in which it will be done will provide the greatest likelihood of success with diuretics and the least likelihood of disaster.

If edema is recognized in its least threatening stages, the measures for its relief will be the simplest, the disorders of water and salt balance incident to its removal will be the most modest, and the success will be obtained without either drama or discomfort. If therapy is delayed until heroic measures are the only ones which will provide sufficient relief in time, regardless of how well chosen the diuretic may be, the nature of the necessary diuretic action will be such that some disturbance due to the diuresis itself is inevitable. The extent of the electrolyte disturbance will very likely be proportionate to the intensity of the therapy.

Therapy should be designed to bring about a normal state of interstitial hydration as well as a restoration of electrolyte homeostasis. I deplore the use of the term "dehydration" because it has implications of desiccation. Tissues properly treated by diuretics are neither dry nor wet; they are normally hydrated. The ideal therapeutic program is one which provides a daily salt-and-water balance, rather than the more commonly weekly or semimonthly salt-and-water statement. Dosage should be regulated accordingly. Frequent injections of relatively smaller doses of mercurial diuretics are both economical and feasible, and a frequent balancing of salt-and-water intake and output may be achieved.

Dosage is better considered in terms of biologic effect than in absolute amounts. There is a difference in initial and maintenance treatment. In the former, parenteral therapy is usually the most efficient. Where time permits, a less than average dose, say 0.5 ml of a mercurial diuretic, can be used to test the patient's response to the drug. In this way, a dose can be determined which will induce an average diuresis of from 1.5 to 2 lb. A larger diuresis is likely to cause cramps or other symptoms due to transient electrolyte disturbance. Where the time is short, the 2 ml dose may be used at the outset. In some relatively resistant cases 3 ml of a mercurial may be a minimal effective dose.

Having induced a state of normal hydration, maintenance therapy must be designed. In some, oral diuretics alone may be satisfactory; in others, a combination with parenteral, and in some only parenteral, diuretics will be satisfactory. In any event, whether oral or parenteral diuretics are used, the doses used should be of such a size and scheduled in such a way that a daily water balance is achieved.

Rational Basis for New Diuretics

The potency of diuretics presently available is adequate for all common needs for diuresis of the type they provide. Indeed, many of the fears about them are based on reactions due to the more than requisite response to some of these agents at the hands of the indiscriminating. The qualities to be sought in new diuretics may be listed, but no available diuretic of adequate potency by the route generally recommended for its use possesses all of these qualities. The ideal diuretic, acting on a basis essentially similar to those now available would have these qualities:

(1) Sustained rather than abrupt violent action.
(2) Reduced capacity for electrolyte upheaval.
(3) Convenience of administration; self-administration (oral, rectal, or subcutaneous).
(4) Decreased toxicity (systemic and local irritant action, especially of the gastrointestinal tract).
(5) Effectiveness where others are ineffectual or contraindicated.
(6) Applicability in cases with a history of allergic reaction to other diuretics.

In evaluating new diuretics that appear on the

market, look for specific data on these issues and remember that early enthusiasms for new diuretics often are not supported by subsequent trials in man. Such discrepancies may arise from the fact that the responses of many animals differ from those in man; in addition, clinical evaluation is determined in the patient with congestive heart failure, a condition which cannot be duplicated in the animal, and bioassay of diuretics in the patient with congestive heart failure usually provides answers which apply much more to potency than to long-continued utility.

Finally, there is the need for diuretics with entirely new mechanisms of action, and hence with different end results; increase in glomerular filtration rate, acceleration of elimination of endogenous metabolites and exogenous materials and the products of their biotransformation; in short, diuretics which actually do stimulate the excretory functions of the kidney.

WALTER MODELL, M.D.
Department of Pharmacology
Cornell University Medical College
New York, New York

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Studies in Diuretic Therapy

Hydrochlorothiazide in the Treatment of Congestive Heart Failure*

ALBERT N. BREST, M.D. *and* WILLIAM LIKOFF, M.D., F.A.C.C.

Philadelphia, Pennsylvania

HYDROCHLOROTHIAZIDE (Esidrix†) is a benzene disulfonamide which is chemically related to chlorothiazide. Studies in animals have shown it to be a very potent diuretic substance. In fact, it has appeared to be more active than chlorothiazide in this respect and also to have a longer duration of action.

This study was undertaken to determine the diuretic effect of hydrochlorothiazide in patients with congestive heart failure.

METHOD

The subjects in this study were divided into the following classes:

Class I. Patients in congestive failure who have never been treated with diuretics.

Class II. Patients who have been in congestive failure and who are controlled only with the aid of diuretics (oral and/or parenteral).

Class III. Patients who have been refractory to treatment for congestive failure, i.e. who have been on a diuretic program without control of congestive failure.

Class I subjects were divided into two groups, one receiving 50 mg hydrochlorothiazide once daily and the other 50 mg twice daily. All class II patients were given 50 mg hydrochlorothiazide twice daily, and all class III subjects received 50 mg three times per day.

Each patient was placed on a 1.0 Gm low-salt diet. Digitalis was given according to need, and all were kept at bed or chair rest while in congestive failure. No one was started on hydrochlorothiazide until his weight had been stabilized on this regimen. Thus, each patient served as his own control.

In addition to daily weights, the following baseline laboratory studies were obtained: serum electrolytes (sodium, potassium, chloride and CO_2), complete blood count, urinalysis, and blood urea nitrogen (BUN). Thereafter, these laboratory studies were repeated at weekly intervals.

FINDINGS

Twenty patients in congestive heart failure were studied. There were five class I subjects; three belonged in class II; and the rest (12) were in the class III category.

Fifteen patients had rheumatic heart disease and two had arteriosclerotic heart disease. In the remaining three cases, the congestive failure was due to interatrial septal defect, primary pulmonary hypertension, and heart disease of undetermined origin.

Diuretic Response: Congestive failure was completely controlled in 16 of the 20 patients. There were four class I, three class II, and nine class III subjects in this group. The individual weight loss in the class I and III patients varied from 5 to 29 pounds and required periods ranging from 3 to 11 days. (See Figs. 1 to 5, which are representative of the diuretic response observed in the class I and III patients in this group.)

* From the Bailey Thoracic Clinic, Philadelphia.

† Esidrix is the registered trademark of Ciba Pharmaceutical Products, Inc., for their brand of hydrochlorothiazide.

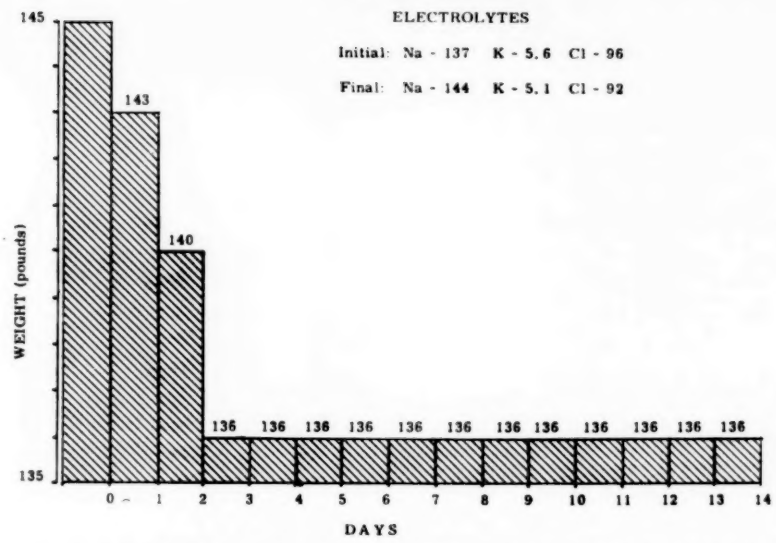

Fig. 1. Weight chart and electrolyte changes in a patient (J. S.) with rheumatic heart disease who had not previously been treated with diuretics. Hydrochlorothiazide, 50 mg once daily, produced complete control of congestive failure in three days.

All three class II patients, who were previously maintained in a compensated state only by means of oral and/or parenteral diuretics, were switched over to hydrochlorothiazide and were maintained without any weight gain. (See Fig. 6, which is representative of the response observed in the class II subjects.)

Two class III patients improved while on hydrochlorothiazide, but their failure could not be completely controlled. The weight loss in these two was 4 and 15 pounds, respectively. In neither case was complete control possible, even though they were subsequently placed on a variety of other diuretic regimens.

One patient was unable to tolerate the drug because of severe nausea and the medication had to be stopped on the second day.

One failed to lose any weight, although kept on the drug for 6 days. This patient did subsequently have a diuretic response when placed on mercurials.

Blood and Renal Effects: All of the patients who were maintained on this drug developed a mild hypochloremia, but in no case did this cause any clinical problem. In no instance were there any significant changes in serum sodium or potassium.

Renal function was checked in all patients by means of weekly BUN determinations and urinalyses. In no instance was there any evidence of renal damage.

Complete blood counts were done at weekly intervals and there were no significant changes in any subject.

Side Effects: The only side effect encountered

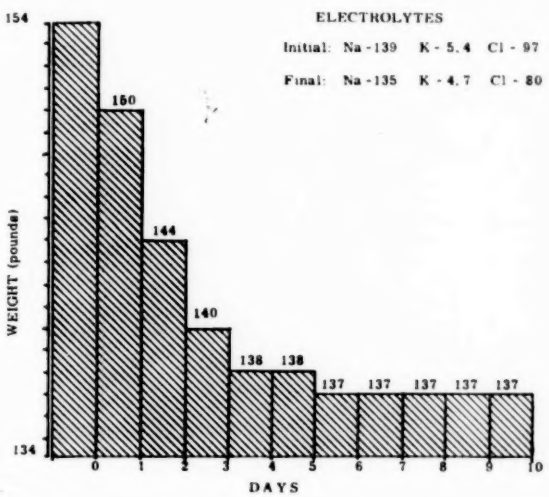

Fig. 2. Weight chart and electrolyte findings in a patient (E. D.) with rheumatic heart disease who had not previously received diuretics. Hydrochlorothiazide, 50 mg twice daily, produced complete control of congestive failure in 6 days.

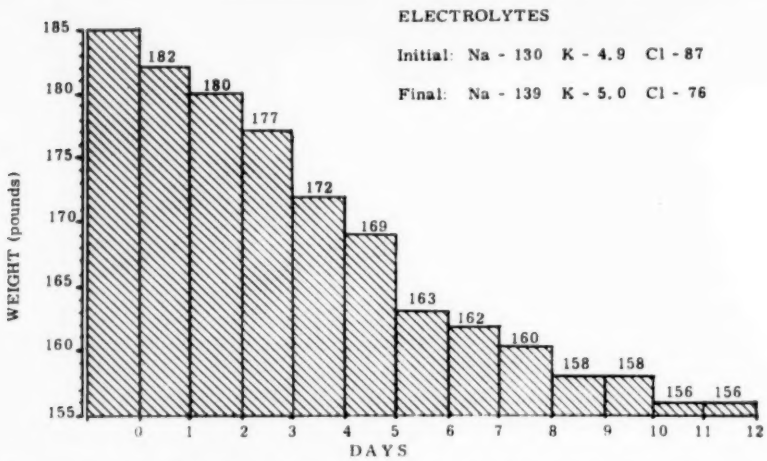

Fig. 3. Patient (H. H.) in severe congestive failure due to arteriosclerotic heart disease who had been on a diuretic program previously without control of congestive failure. Hydrochlorothiazide, 50 mg three times daily, produced complete control in 11 days.

was nausea. This occurred in 3 of the 20 subjects. Two were able to continue taking medication in spite of the nausea. However, the drug had to be stopped in the third patient because of this complaint.

Discussion

Hydrochlorothiazide has been shown experimentally to be a potent diuretic substance. On the basis of a milligram for milligram comparison hydrochlorothiazide has been found to be roughly twenty times more potent than chlorothiazide in at least one animal species.

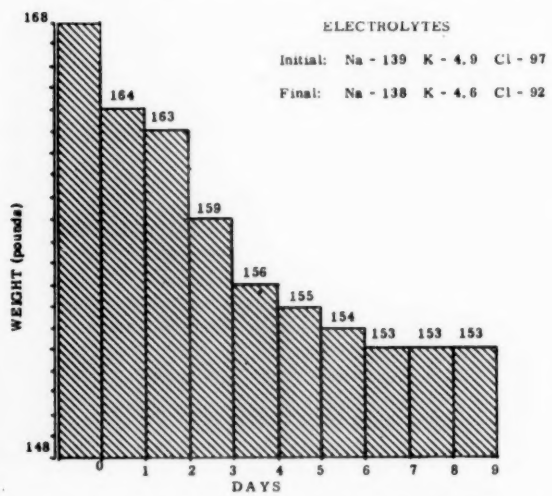

Fig. 4. Patient (A. T.) in congestive failure due to heart disease of undetermined origin who had been on a diuretic program previously without control of congestive failure. Hydrochlorothiazide, 50 mg three times daily, produced complete control in 7 days.

Pharmacologic studies with this drug have shown that the chloride ion is the major anion excreted in the urine. As a comparison, doses of hydrochlorothiazide in the dog which are equipotent with chlorothiazide in regard to the excretion of water, sodium, and potassium have produced a significantly greater effect on the diuresis of chloride. This suggests that the two drugs may operate through different mechanisms, though the exact mode of action still remains unproved.

Preliminary studies in humans treated with hydrochlorothiazide for congestive heart failure and hypertension have failed to show any deleterious hematologic effects.

One investigator[1] observed a rise in nonprotein nitrogen (NPN) and other evidences of uremia during the administration of hydrochlorothiazide to patients with kidney dysfunction associated with hypertension. However, an elevated BUN would not appear to be an absolute contraindication to the use of this drug, since a fall in BUN has been reported[1] in a series of cases of congestive heart failure after treatment with hydrochlorothiazide. Complete blood counts, urinalyses, and BUN determinations were performed weekly in all hospital

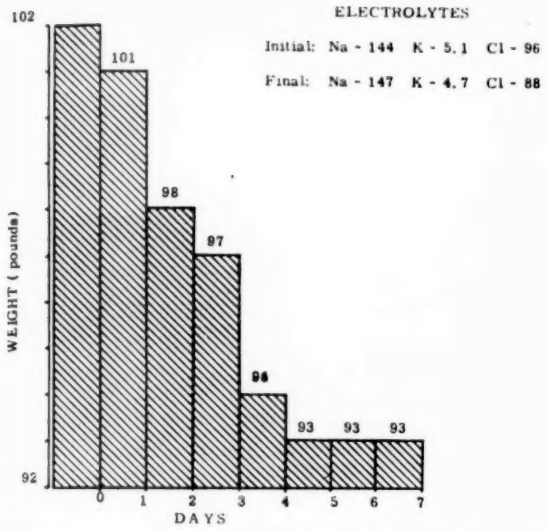

Fig. 5. Weight chart and electrolyte changes in a patient (M. C.) with rheumatic heart disease, who had been on a diuretic program previously without control of congestive failure. Complete control was achieved in 5 days, using 50 mg hydrochlorothiazide three times a day.

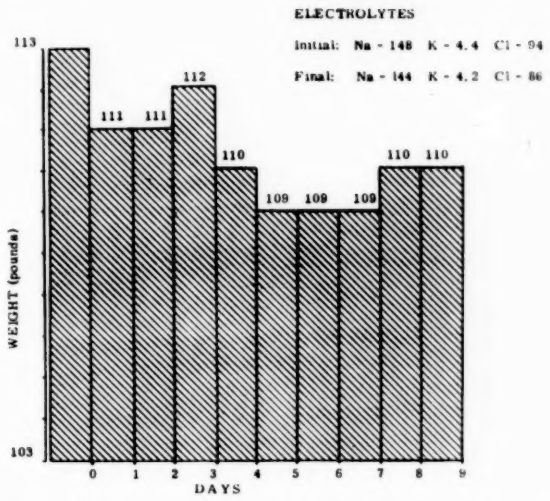

Fig. 6. Patient (S. L.) with rheumatic heart disease whose congestive failure was controlled previously only by means of parenteral diuretics. Hydrochlorothiazide, 50 mg twice daily, maintained her in a compensated state.

patients in this series, and in no instance were any deleterious changes noted.

Serum and urinary electrolyte studies in humans reveal that hydrochlorothiazide markedly increases the excretion of water, sodium, and chloride, and increases to a lesser extent the excretion of potassium, although significant reductions of serum potassium have been reported. All of the subjects in this series developed a mild hypochloremia, but in no case did this cause any clinical signs or symptoms. In no instance were there any significant changes in serum potassium or sodium.

Side effects reported to date by other investigators have been principally nausea, anorexia, and a sensation of weakness. Generalized urticaria has been reported in one case. The only side effect encountered in this series was nausea, which occurred in three of the 20 subjects. However, only in one of these three patients was it necessary to discontinue the drug because of this side effect.

This preliminary report on a new oral diuretic, hydrochlorothiazide, would appear to indicate that it is a very potent diuretic substance, as evidenced particularly by its effect on class III subjects who had been refractory to other diuretic regimens. Investigations are now being continued to determine the minimal effective dose, long-term follow-up results, and comparative effect of this drug with other oral and parenteral diuretics.

Summary

A new oral diuretic, hydrochlorothiazide, was studied in 20 patients with congestive heart failure. In 16 of the 20 subjects, the congestive failure was successfully controlled with the aid of this diuretic. Two patients were improved, but their congestive failure was not completely controlled. One patient was unable to tolerate the drug because of severe nausea, and one patient failed to show any diuresis while on this medication.

All patients who were maintained on this medication developed a mild hypochloremia, but no significant changes in serum sodium or potassium were observed. No deleterious hematologic or renal changes occurred.

The only side effect encountered was nausea, and only in one patient was this severe enough to prevent the continued administration of this medication.

Reference

1. Ciba Pharmaceutical Products, Inc., Clinical Investigation Division. Personal communications, 1958.

Laboratory and Clinical Observations on Chlorazanil,* a Nonmercurial Orally Effective Diuretic Agent†

RALPH V. FORD, M.D., J. B. ROCHELLE, III, M.D., ALLEN C. BULLOCK, M.D., C. L. SPURR, M.D.,‡
CARROLL HANDLEY, PH.D., *and* JOHN H. MOYER, M.D., F.A.C.C.§
Houston, Texas

DRUGS to promote the excretion of water in edematous states of varied etiology form an essential part of the equipment of every practitioner. Although the common denominator of all types of edema appears to be sodium retention by the kidney, many factors may be operative; viz., cardiac failure, decreased renal function, excess salt-retaining steroids, excess antidiuretic hormone, serum electrolyte imbalance, etc. In view of the multiplicity of factors in pathogenesis, it is not strange that the investigator should explore a variety of agents capable of inhibiting the abnormal renal retention of salt and water. Attention was called for the first time by Lipschitz over 13 years ago[1] to a new group of substances possessing diuretic effects. These were triazine derivatives which were toxic, but which furnished an objective for chemical development which has culminated in the development of chlorazanil (N-para-chlorophenyl - 2,4 - diamino - s - triazine hydrochloride). This compound possesses the strongest diuretic effect with the least toxicity and furnishes the subject for this report.

The drug has been studied in men and dogs for its effect on the excretion of water and electrolytes and for its influences on renal hemodynamics. This includes the establishment of a dose response curve and subsequent calculation of its potency relative to a standard diuretic (meralluride or Mercuhydrin) as well as the clinical responses following chronic therapy. Additional studies have been made on the drug in combination with aminophylline. The rationale for this approach and its application to other diuretic agents have been previously elaborated.[2–7]

METHODS AND MATERIALS

(A) LABORATORY OBSERVATIONS

Five groups of dogs received chlorazanil and one group (group VI) received chlorazanil in combination with aminophylline. Dogs in group I and IV received chlorazanil as a single intravenous dose. The dogs in groups II, III, and V received chlorazanil orally.

Group I: Thirty-two nonhydrated dogs, which were anesthetized with 30 mg/kg of pentobarbital, were given single intravenous doses of chlorazanil. After suitable control periods, each of four doses was administered

* N-p-chlorophenyl-2,4-diamino-s-triazine, marketed in Europe as Orpidan or Neo-Urofort. Supplied as Riker-545 (Daquin) and SKF-3195.

† From the Departments of Medicine and Pharmacology, Baylor University College of Medicine, and the Medical Service, Veterans Administration Hospital, Houston, Texas.

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‡ Present address: Bowman Gray School of Medicine, Winston-Salem, North Carolina.
§ Present address: Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

to eight different dogs, i.e., 2 mg/kg, 4 mg/kg, 8 mg/kg, and 16 mg/kg.* Urines were collected in 20-minute periods for six hours and analyzed for sodium, potassium, and water excretion.

Group II: Twelve dogs received divided oral doses of chlorazanil. They were allowed to take water *ad lib.* Four dogs were each given 10 mg/kg, four were given 20 mg/kg, and four dogs received 40 mg/kg. Half the dose was administered at the beginning of a 24-hour period and the other half was administered 12 hours later. Urines, collected as single 24-hour specimens, were analyzed for sodium and potassium, and the volumes were noted.

Group III: Eight dogs were given 20 mg/kg per day in two divided doses of chlorazanil for six successive days in order to determine the persistence of the diuretic effect. Urine was collected as single 24-hour specimens. The dogs had free access to water throughout the study. The dietary sodium was not standardized for the group but was kept constant for each dog, being approximately the same during the control period as during the period of drug administration.

Group IV: Observations were made on renal hemodynamics in 8 dogs anesthetized with 30 mg/kg of pentobarbital. Methods and technics have been described previously.[8,9] Observations were made before and for three hours after drug administration, intravenously in a dose of 8 mg/kg. Creatinine was used to determine glomerular filtration rate and para-aminohippurate was used to determine renal plasma flow. Blood pressure was measured by direct intra-arterial manometry. Concurrent observations were made on water, sodium, and potassium excretion.

Group V: Similar observations on renal hemodynamics were made on five dogs in the control state and one week later after the animals had been given 20 mg/kg per day of chlorazanil as a single oral dose. The last measurements were made two hours after administration of the last dose.

Group VI: Five anesthetized dogs received a combination of chlorazanil (10 mg/kg) and aminophylline (25 mg/kg) given intravenously as a single dose. Observations on glomerular filtration rate, renal plasma flow, water excretion, and sodium excretion were made[8,9] in the control state and for three hours after the drug administration.

(B) CLINICAL OBSERVATIONS

(*I*) *Electrolyte Excretion Patterns:* The effect of chlorazanil on the urinary excretion of various electrolytes and water was observed in five patients with well-controlled congestive heart failure. Each of the patients drank 3,000 ml of water a day. This was allotted fractionally to assure a constant water intake throughout the day. Urine was collected under oil in six periods per 24 hours (three two-hour periods and three six-hour periods). These specimens were analyzed for sodium, potassium, chloride, phosphate, titratable acidity, ammonia, bicarbonate, total solute, and volume. Two of the three patients received 600 mg of chlorazanil as a single oral dose at 6:00 a.m.; the third patient received 600 mg at 6:00 a.m. and 6:00 p.m. of the same day.

Dose-Response Relationships: A dose-response curve was determined for chlorazanil. The drug was given orally in a single dose starting with 150 mg. Subsequently, the dose was increased to 300 mg, 600 mg, and 800 mg until it produced nausea and vomiting in over 25 per cent of the patients. Since doses of 300 and 600 mg produced optimum sodium excretion without toxicity, the bioassay of 10 patients was limited to these two dose levels. A single oral dose of 600 mg of chlorazanil–200 mg of aminophylline was administered to 10 patients to determine the effect of the drug in combination with aminophylline on sodium and water excretion.

Potency Estimate of Chlorazanil Compared to a Standard Diuretic: A standard analysis of variance was performed on the results obtained with chlorazanil and the standard, meralluride (Mercuhydrin). Since these two dose-response curves were parallel, linear, and without significant error, a potency estimate of chlorazanil, compared to meralluride as "one," was made.

(*II*) *Bioassay for Potency in Man:* The technics of this study have been described previously.[2] Briefly, ten male patients with a roughly equivalent degree of well controlled heart failure were the subjects of the study for this drug. These patients were maintained in an air-conditioned metabolic ward under the observation of trained personnel. With the exception of diuretic agents, all medications required for control of the heart failure of these patients were continued throughout the study. The patients were allowed to be ambulatory about the metabolic ward. The diet contained approximately 300 g of carbohydrate, 100 g of protein, and 100 g of fat with a total of 2,800 cal/day. This diet was varied somewhat with the caloric requirements of the individual patient. The sodium content of each patient's diet was exactly 50 meq/24 hours. The patients drank 3 liters of distilled water every day. They were allowed to equilibrate on this diet until each patient excreted a constant amount of sodium, which approximated 90 per cent (45 meq/24 hours) of their dietary sodium. The diuretic agent to be tested was then administered. Before the administration of the next dose of the diuretic agent, 4–6 days were allowed for the patient to equilibrate by the restoration of sodium and water stores. Each patient was weighed before breakfast and after voiding. Urine was collected in 24-hour periods and analyzed for sodium, potassium, chloride, volume, and creatinine (as a measure of the completeness of the collection). Other routine studies included plasma electrolytes, electrocardiograms, and chest x-ray on each patient.

(*III*) *The Effect of Chlorazanil After Chronic Daily Therapy:* Chlorazanil was administered for five days in single daily oral doses of 300 mg to ten patients with

* A dose of 64 mg/kg was administered to six dogs, but this proved to be toxic and, consequently, diuretic studies were not done at this dose level.

TABLE I

The Effect of Single Intravenous Doses of Chlorazanil on Water and Electrolyte Excretion in Dogs

Body weight (kg)	Urine flow (ml/min)								Urine sodium (μeq/min)								Urine potassium (μeq/min)							
	C	D_1	D_2	D_3	D_4	D_5	D_6	Max	C	D_1	D_2	D_3	D_4	D_5	D_6	Max	C	D_1	D_2	D_3	D_4	D_5	D_6	Max
The response to 2 mg/kg given to eight dogs																								
Mean 12.7	0.4	0.8	1.0	1.0	0.9	0.6	0.6	1.3	12	71	114	104	106	70	67	149	9	14	13	11	11	11	11	19
% of control		200	250	250	225	150	150	325		592	950	867	883	583	558	1242		156	144	122	122	122	122	211
P value less than		0.20	0.10	0.10	0.05	0.20	0.05	0.05		0.20	0.10	0.05	0.05	0.05	0.10	0.05		0.01	0.20	0.30	0.20	0.50	0.50	0.01
The response to 4 mg/kg given to eight dogs																								
Mean 13.3	0.2	0.5	0.6	0.5	0.5	0.6	0.6	1.0	12	52	86	69	95	102	116	198	4	11	6	5	6	6	10	16
% of control		250	300	250	250	300	300	500		433	717	575	792	850	967	1650		275	150	125	150	150	250	400
P value less than		0.01	0.001	0.05	0.05	0.10	0.10	0.01		0.01	0.01	0.05	0.05	0.10	0.10	0.05		0.05	0.30	0.50	0.40	0.20	0.10	0.001
The response to 8 mg/kg given to eight dogs																								
Mean 12.3	0.2	0.5	0.7	0.7	0.7	0.7	0.7	1.1	6	66	105	110	121	109	91	189	6	14	7	7	8	9	10	18
% of control		250	350	350	350	350	350	550		1100	1750	1833	2017	1817	1517	3150		233	117	117	133	150	167	300
P value less than		0.05	0.01	0.01	0.01	0.05	0.05	0.01		0.05	0.05	0.05	0.01	0.01	0.05	0.01		0.20	0.50	0.50	0.50	0.40	0.50	0.05
The response to 16 mg/kg given to eight dogs																								
Mean 12.2	0.3	0.9	1.1	0.9	0.8	0.8	0.7	1.4	9	109	186	141	149	137	118	234	10	20	12	9	9	10	10	22
% of control		300	367	300	267	267	233	467		1211	2067	1567	1656	1522	1311	2600		200	120	90	90	100	100	220
P value less than		0.20	0.05	0.05	0.10	0.10	0.20	0.01		0.10	0.05	0.01	0.05	0.05	0.05	0.01		0.05	0.50	0.50	0.50	0.50	0.50	0.01

Key to Abbreviations: C = Control. D_1 = First 20 min after drug. D_2 = 30 min after drug. D_3 = 2 hr after drug. D_4 = 3 hr after drug. D_5 = 4 hr after drug. D_6 = 5 hr after drug. Max = Maximum response during any single 20-min period.

compensated cardiac failure. Urine was collected in 24-hour specimens and analyzed for sodium and water. The blood of each of these patients was analyzed for serum sodium, potassium and chloride concentrations, carbon dioxide combining power and for blood urea nitrogen before and after administration of 300 mg of chlorazanil a day for five days.

(IV) The Effect of Chlorazanil on Nitrogen Balance and Renal Function: In another group of 20 hypertensive nonedematous outpatients, ten were given 300 mg daily as a single oral dose and ten were given 300 mg twice daily for 21 days. The patients were seen at weekly intervals, at which time blood urea nitrogen determinations were done to compare with baseline studies obtained prior to the institution of therapy.

After this study was complete, it was found advisable to study more precisely the effect of chlorazanil on the blood urea nitrogen concentration. Four patients were the subjects of balance studies for sodium, potassium, chloride, nitrogen, phosphate and water with concomitant observations of plasma creatinine and urea nitrogen, as well as measurements of 24-hour endogenous creatinine clearance (based upon single plasma creatinine determination).

The patients were observed for 20 days, the first five of which constituted a control period, the next ten the drug-treatment period and the next five a post-treatment period. Two patients received 150 mg twice daily and two received 300 mg twice daily during the drug-treatment periods. Dietary intake was constant for sodium, nitrogen, water, and calories. Urine and fecal excretions were analyzed for the moieties described above.

To gain broader clinical implications of this problem, another 20 outpatients (from Hypertensive Clinic) with well-controlled congestive failure were given chlorazanil 150 mg twice daily for three weeks. They were observed for changes in blood urea nitrogen concentration, plasma creatinine concentration, endogenous creatinine clearance (two consecutive one-hour specimens after hydration), phenolsulfonphthalein excretion (two consecutive 0–15 minute specimens after intravenous injection), urinary constituents and body weight. No change was made in previous rendered therapy (antihypertensive agents and digitalis).

Results

(A) Laboratory Observations

Group I: When a single dose of chlorazanil was given intravenously to 32 anesthetized, nonhydrated dogs, there was a significant increase in sodium and water excretion appearing within 20 minutes after drug administration and persisting for five hours or more. The maximum increase in water excretion due to chlorazanil was no greater with a dose of 16 mg/kg than with one of 4 mg/kg but the diuretic response was of longer duration at the higher dosages. Potassium excretion was increased

TABLE II

THE ACUTE EFFECT OF ORAL DOSES OF CHLORAZANIL ON WATER AND ELECTROLYTE EXCRETION IN DOG

	Body Wt. Kg.	Urine Volume cc/min.				Urine Sodium μEq/min.				Urine Potassium μEq/min.		
		C	D	PD		C	D	PD		C	D	PD
5 mgm/kg given orally twice a day for one day to four dogs												
Mean	10.8	0.27	0.42	0.22	23	25	20		9	18	16	
% of Control			156	81		109	87			200	178	
P Value			N.S.	N.S.		N.S.	N.S.			N.S.	N.S.	
10 mgm/kg given orally twice a day for one day to four dogs												
Mean	9.0	0.20	0.34	0.33	15	28	16		9	14	11	
% of Control			170	165		187	107			156	122	
P Value			N.S.	N.S.		<.1	N.S.			N.S.	N.S.	
20 mgm/kg given orally twice a day for one day to four dogs												
Mean	9.3	0.15	0.44	0.21	8	24	5		5	8	5	
% of Control			293	140		300	63			160	100	
P Value			<.1	N.S.		<.05	N.S.			N.S.	N.S.	

Key: C - Two - 24 hour Control periods (average)
D - Twenty-four hour period during drug administration
PD - Twenty-four hour period following drug administration

only slightly and this effect was of short duration (Table I).

Group II: When the drug was given orally in two divided doses, the diuretic effect was less dramatic than following intravenous administration. The effect on water excretion was just as great as, if not greater than, the increase in sodium excretion rather than the increase in water excretion being secondary to the increased sodium loss. The dose of 5 mg/kg given twice a day did not appear to increase sodium excretion despite a water diuresis, whereas a dose in excess of 10 mg/kg given twice a day appeared to increase both water and sodium excretion. There was no consistent effect on potassium excretion (Table II).

Group III: When chlorazanil was given continuously for six days, the increase in water excretion persisted throughout the period of observation. The effect on sodium excretion was variable from day to day but showed a slight increase above the control observations (Table III).

Group IV: When given intravenously to eight anesthetized dogs, chlorazanil did not have a hypotensive effect. In fact, there was a slight increase in blood pressure one hour after drug administration. Glomerular filtration rate was not altered when the chlorazanil was dissolved in 150 ml of saline. There was a slight reduction in renal plasma flow, but this was not significant. However, when the drug was administered in a concentrated form in 10 ml of saline, glomerular filtration rate and renal plasma flow were both depressed one hour or more following drug administration (Table IV).

Group V: When the chlorazanil was given as a single oral dose to five dogs, there was no effect on glomerular filtration for a period of four hours after drug administration. Renal plasma flow was not altered for a period of two hours after drug administration but, after four hours, there was a moderate reduction. This latter response was probably due to the prolonged anesthesia (Table V).

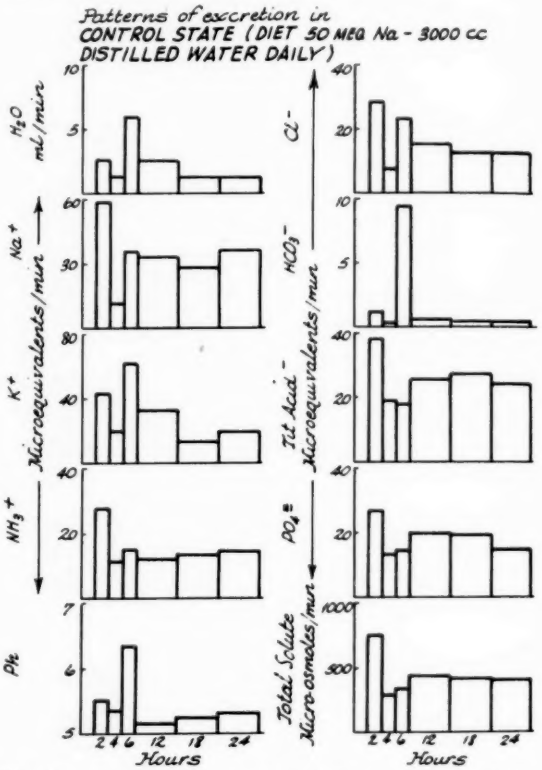

Fig. 1. Average urinary electrolyte excretion pattern found in five patients with well-compensated congestive heart failure.

TABLE III

THE CHRONIC EFFECT OF ORAL DOSES OF CHLORAZANIL ON WATER AND ELECTROLYTE EXCRETION

(10 mgm/kg given orally twice a day for six days to eight dogs)

	Wt. Kg.	Urine Volume cc/min.							Sodium Excretion μEq/min.							Potassium Excretion μEq/min.						
		C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6
Mean	10.8	0.19	0.30	0.45	0.51	0.49	0.57	0.47	16	27	36	23	21	26	16	9	12	12	10	11	12	12
% of Control			158	237	268	258	300	247		169	225	144	131	163	100		133	133	111	122	133	133
* P Value less than			.05	.10	.10	.05	.05	.10		.05	.10	.30	.20	.20	.50		.20	.20	.50	.40	.10	.30

Key: C - Control observations - average of two 24 hour urine collection periods.
D_1 to D_6 - Successive 24 hour urine collection periods.
* - $t = \bar{x}\sqrt{\frac{n(n-1)}{S_x^2}}$

TABLE IV

THE RENAL RESPONSE TO CHLORAZANIL GIVEN INTRAVENOUSLY

(8 mgm/kg given in 150 cc saline to eight dogs)

	Period	Mean	% of control	P Value less than
Mean blood pressure mm. Hg.	C	114		
	D_1	112	98	.50
	D_2	120	105	.20
	D_3	126	111	.01
	D_4	128	112	.01
Glomerular Filtration Rate (cc/min.) (Creatinine Clearance)	C	38		
	D_1	37	97	.50
	D_2	35	92	.30
	D_3	35	92	.20
	D_4	37	97	.50
Renal Plasma Flow (cc/min.) (C PAH)	C	195		
	D_1	218	112	.30
	D_2	162	83	.05
	D_3	157	81	.30
	D_4	159	82	.10
Hemato-crit	C	36		
	D_1	37	103	.50
	D_2	37	103	.40
	D_3	37	103	.50
	D_4	36	100	.50
Urine Volume (cc/min.)	C	1.6		
	D_1	3.0	188	.01
	D_2	2.8	175	.10
	D_3	2.6	163	.05
	D_4	2.5	156	.05

Key: C - Control Observations
D_1 - Observations immediately after administration of Chlorazanil
D_2 - Observations one hour " " " "
D_3 - Observations two hours " " " "
D_4 - Observations three hours " " " "

(Average weight = 11.8 kg.)

TABLE V

THE RENAL RESPONSE TO CHLORAZANIL GIVEN ORALLY

(20 mgm/kg given orally two hours before anesthetizing to five dogs)

	Period	Mean	% of control	P Value less than
Mean blood pressure mm. Hg.	C	104		
	D_1	114	110	.20
	D_2	98	94	.40
	D_3	109	105	.20
	D_4	117	113	.10
Urine Volume (cc/min.)	C	0.7		
	D_1	0.7	100	.50
	D_2	2.0	286	.01
	D_3	2.1	300	.05
	D_4	2.3	329	.05
Glomerular Filtration Rate (cc/min.) (Creatinine Clearance)	C	48		
	D_1	47	98	.50
	D_2	48	100	.50
	D_3	43	90	.50
	D_4	44	92	.30
Renal Plasma Flow (cc/min.) (C PAH)	C	299		
	D_1	214	72	.50
	D_2	297	99	.50
	D_3	213	71	.20
	D_4	184	62	.10
Hemato-crit	C	41		
	D_1	35	85	.30
	D_2	39	95	.50
	D_3	40	98	.50
	D_4	37	90	.20

Key: C - Control Observations
D_1 - Observations (average of two 10-minute periods) immediately after anesthetization and two hours after administration of Chlorazanil.
D_2 - Observations two hours and 30 minutes after administration of Chlorazanil
D_3 - Observations three hours after administration of Chlorazanil.
D_4 - Observations four hours after administration of Chlorazanil.

(Average weight = 13.2 Kg.)

Group VI: Aminophylline did not appear to alter the renal hemodynamic response to chlorazanil in five anesthetized dogs. Likewise, the effect of chlorazanil on water and sodium excretion was not affected by aminophylline.

(B) CLINICAL OBSERVATIONS

(*I*) *Electrolyte Excretion Patterns:* The patterns of average excretions of urinary constituents determined in five patients with well-controlled congestive heart failure are presented in Figure 1. Administration of 600 mg of chlorazanil as a single oral dose (Figs. 2 and 3) produced primarily a significant increase in sodium, water, and chloride excretion. There was a moderate increase in bicarbonate excretion. Potassium excretion was sometimes increased. Ammonia excretion was decreased during the time of greatest natriuresis. Phosphate and titratable acidity excretion were depressed also. The total solutes were slightly increased in terms of micro-osmols per minute, but the concentration of solutes in terms of milliosmols per liter was less than the concentration seen with comparably potent diuretic agents. The onset of these effects occurred approximately two hours after administration of the drug and lasted for 12 to 18 hours. When 600 mg was given twice at 12-hour intervals, there was a noticeable but delayed effect from the second dose which was of a lesser magnitude than the effect of the first dose (Fig. 4).

(*II*) *Bioassay for Potency in Man: Dose-response relationships:* Chlorazanil 300 mg given as a single oral dose caused an increase in sodium excretion of 11 meq and water excretion of 0.14 *l*/24 hours. Following the administration of 600 mg there was an increase in sodium excretion of 60 meq/24 hours and an increase

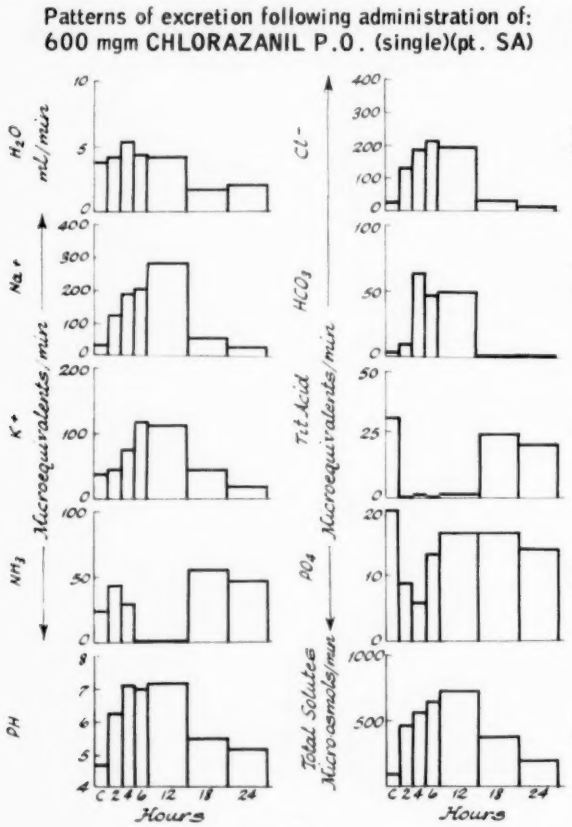

Fig. 2

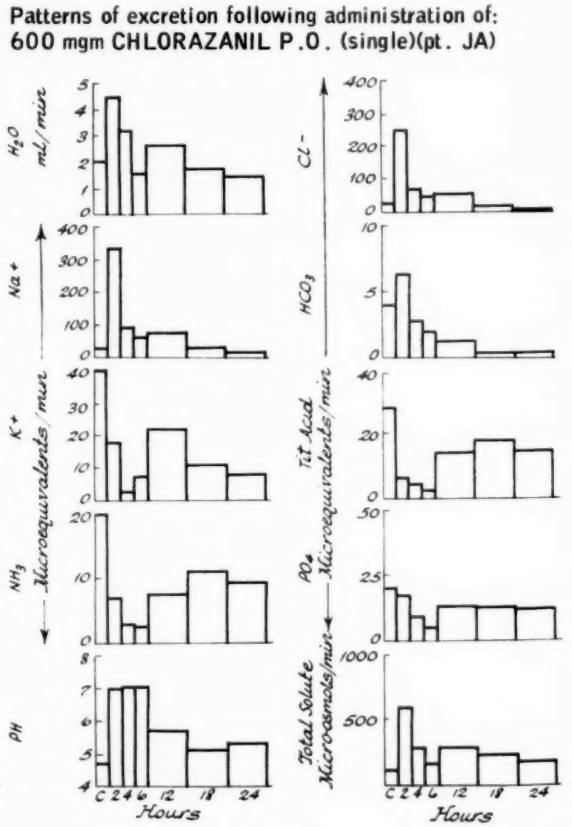

Fig. 3

Fig. 2 and 3. Electrolyte excretion pattern in the urine following a single dose of chlorazanil emphasizes a major effect in augmenting the excretion of water, sodium, and chloride with a lesser effect on bicarbonate.

TABLE VI

THE EFFECT OF CHLORAZANIL ON SODIUM AND WATER EXCRETION IN MAN

(Average values for 10 patients)

Dose	Sodium Excretion (mEq/24 hrs.)			Urine Volume (liters/24 hrs.)		
	C	D	I	C	D	I
300 mgm.	48	59	11	3.31	3.45	0.14
P Value less than			.01			.01
600 mgm.	49	109	60	3.53	3.92	0.39
P Value less than			.001			.001

Key: C - Control sodium excretion or water excretion

D - Drug sodium or water excretion

I - Increase in sodium or water excretion

TABLE VII

COMPARISON OF THE EFFECT OF CHLORAZANIL ALONE AND IN COMBINATION WITH AMINOPHYLLINE ON SODIUM AND WATER EXCRETION IN MAN

(Average values for 10 patients)

Drug	Increase in Sodium Excretion (mEq/24 hrs.)	Increase in Urine Volume (liters/24 hrs.)
Chlorazanil (600 mgm.)	60	0.39
P Value less than	.001	.001
Chlorazanil (600 mgm.) plus Aminophylline (200 mgm.)	57	0.44
P Value less than	.001	.001
P Value between the two means	N.S.	N.S.

in water excretion of 0.39 *l*/24 hours (Table VI). The increase in chloride excretion roughly paralleled the increase in sodium excretion while potassium excretion was not consistently altered. Chlorazanil 600 mg in combination with 200 mg of aminophylline as a single oral dose produced an increase in sodium excretion of 57 meq/24 hours and an increase in water excretion of 0.44 *l*/24 hours. A Student's "t" test showed that the differences in increased sodium and water excretion between 600 mg of chlorazanil alone and 600 mg of chlorazanil with 200 mg of aminophylline were not significant (Table VII).

Potency estimate of chlorazanil: An analysis of variance was performed comparing chlorazanil to meralluride (Mercuhydrin), the standard. The two dose-response curves were parallel and the error in the experimental trials[2] was not significant (Fig. 5). A calculation based on sodium excretion showed chlorazanil to be 0.49 in potency, compared to meralluride, the standard, if meralluride is taken as "one." Expressed in another way, 600 mg of chlorazanil orally is equal to 1 cc (40 mg of Hg) of meralluride (intramuscularly) in producing an increased sodium excretion. The potency of chlorazanil based on water excretion and compared to meralluride as "one" was found to be 2.2, suggesting a greater effect on water excretion than with comparably potent diuretic agents.

(III) The Effect of Chlorazanil After Chronic Daily Therapy (Table VIII): As a single dose of 300 mg per day, chlorazanil produced continuous response on five successive days in 10 patients (Fig. 6). There were no significant changes in serum electrolyte concentration or in blood urea nitrogen concentration after five days of administration (Fig. 7).

The effect of chronic chlorazanil administration on blood urea nitrogen in 10 nonedematous hypertensive patients is presented in Table IX. The mean values for blood urea nitrogen in the group receiving 300 mg daily were 20.4 mg% in the control state, 31.4 after one week, and 31.9 after three weeks of drug therapy. In the group receiving 600 mg daily, the mean control blood urea nitrogen value was 21.8 mg%. This mean value rose to 45.9 after one

week and was 43.6 after three weeks of drug therapy. Six of ten patients receiving 300 mg daily and eight of ten patients receiving 300 mg twice daily demonstrated moderate increases in blood urea nitrogen. In no instance was there an alteration of hematocrit contemporary with this elevation of blood urea nitrogen. Side effects seen, more often with the larger dosage, were anorexia, occasional vomiting, potentiation of "ganglionic blockade" (antihypertensive therapy), and generalized weakness.

(IV) The Effect of Chronic Chlorazanil Administration on Nitrogen Balance and on Renal Function Studies: The significant results of the balance studies are presented in Figures 8 and 9. These are the average values for two nonedematous hypertensive patients each at two dosage levels, 300 mg and 600 mg daily. During the daily administration of 300 mg of chlorazanil, there was a slight increase in urinary sodium, producing a slightly negative balance. Urinary volume increased to a greater degree and the patients complained of thirst while a disproportionately small weight loss was observed. Nitrogen balance became progressively positive after the fifth day of drug administration. The endogenous creatinine clearance depression paralleled the positive nitrogen balance, while blood urea nitrogen concentrations were elevated. During the administration of 600 mg of chlorazanil daily, similar changes were observed but were of greater magnitude: sodium balance became more negative, water balance even more

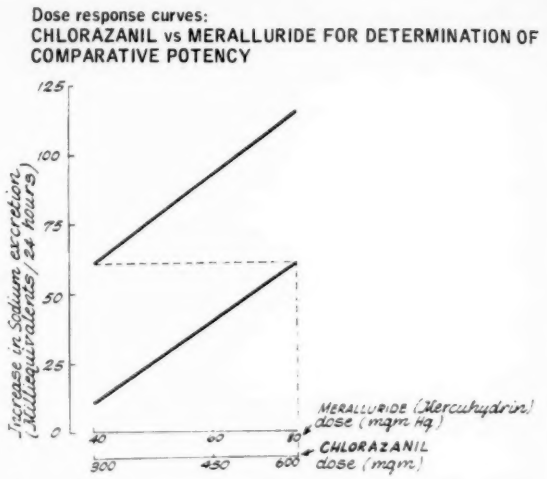

Fig. 5. The dose response curves for meralluride and chlorazanil indicate that approximately 600 mg of the latter orally is equivalent to 1 ml of meralluride intramuscularly as a natriuretic agent.

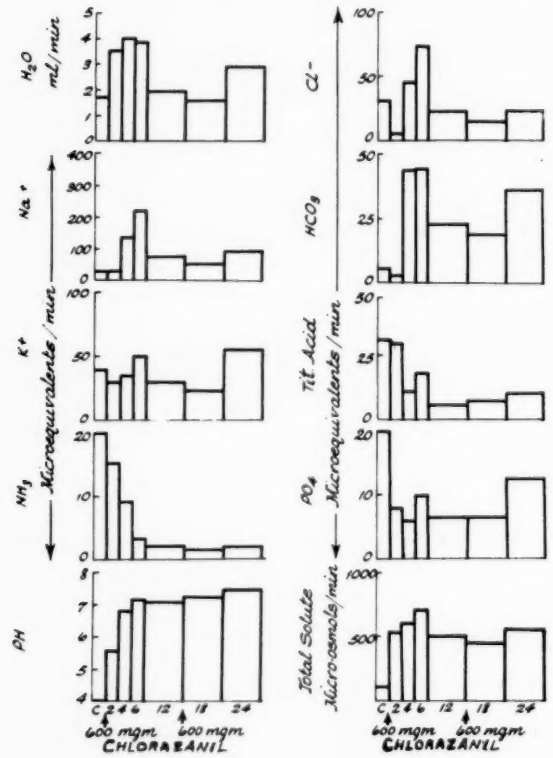

Fig. 4. Following the second dose of the drug in a 12-hour period, there is an additional augmentation of diuresis and natriuresis.

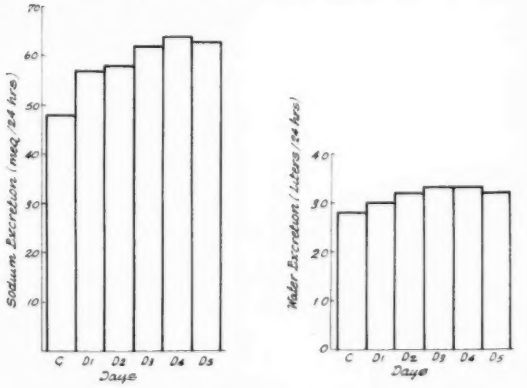
THE EFFECT OF CHLORAZANIL HYDROCHLORIDE ON SODIUM AND WATER EXCRETION - 300 mgm per day for 5 consecutive days
Sodium Excretion (meq/24 hrs)
Water Excretion (Liters/24 hrs)
C D1 D2 D3 D4 D5
Days

Fig. 6. Daily doses of chlorazanil are repetitively effective in producing water and sodium loss (average of data from 10 patients with compensated congestive failure).

TABLE VIII

THE EFFECT OF CHLORAZANIL 300 MGM. DAILY IN MAN FOR FIVE CONSECUTIVE DAYS ON THE EXCRETION OF SODIUM AND WATER AND PLASMA ELECTROLYTES AND BLOOD UREA NITROGEN (Average values for 10 patients)

	C	D_1	D_2	D_3	D_4	D_5
Urine						
Sodium (mEq/24 hrs)	48	57	58	62	64	63
P Value less than		.01	.01	.01	.01	.01
Volume (liters/24 hrs)	2.8	3.0	3.2	3.3	3.3	3.2
P Value less than		.01	.01	.01	.01	.01
Blood						
Sodium (mEq/liter)	144					143
P Value						N.S.
Potassium (mEq/liter)	4.8					4.8
P Value						N.S.
Chloride (mEq/liter)	102					104
P Value						N.S.
Carbon dioxide combining power (mEq/liter)	29					29
P Value						N.S.
Urea nitrogen (mgms. %)	20					24
P Value less than						.50

Key:

C - Control
D_{1-5} - Consecutive days of drug administration

negative, while nitrogen balance became more positive and was accompanied by depression of creatinine clearance and elevation of blood urea nitrogen concentration. Changes in phosphate balance paralleled those in nitrogen balance while changes in chloride balance paralleled those in sodium balance. Potassium balance was not significantly altered.

Among the 20 hypertensive outpatients with well-controlled cardiac failure, eight showed a

THE EFFECT OF CHLORAZANIL HYDROCHLORIDE ON SERUM ELECTROLYTES

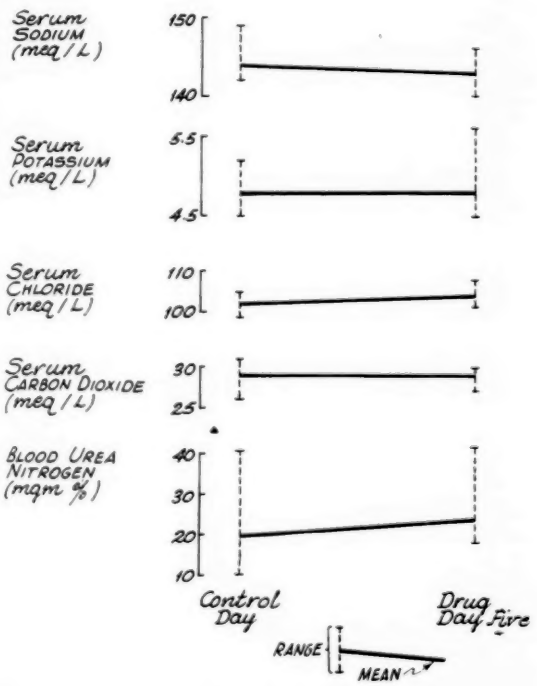

Fig. 7. Serum electrolytes after five days of chlorazanil therapy are not significantly altered except for those directional shifts due to dehydration.

TABLE IX

EFFECT OF CHRONIC ORAL ADMINISTRATION OF CHLORAZANIL ON BLOOD UREA NITROGEN

Patient	Blood Urea Nitrogen C	D_1	D_3	Dose (mg/day)
1. L. A.	28	28	29	300
2. J. H.	18	17	30	300
3. R. H.	18	34	35	300
4. S. C.	17	20	16	300
5. A. L.	10	10	11	300
6. J. L.	23	19	22	300
7. J. E.	27	48	46	300
8. D. T.	24	74	48	300
9. O. T.	19	34	32	300
10. A. G.	20	30	50	300
Mean	20.4	31.4	31.9	
11. B. W.	11	34	22	600
12. C. A.	27	26	35	600
13. D. B.	23	42	38	600
14. R. B.	23	47	52	600
15. D. C.	10	37	29	600
16. E. G.	14	50	44	600
17. W. M.	15	62	48	600
18. J. R.	17	17	16	600
19. J. W.	32	66	70	600
20. J. R.	46	78	82	600
Mean	21.8	45.9	43.6	

C - Control
D_1 - After one week of therapy
D_3 - After three weeks of therapy

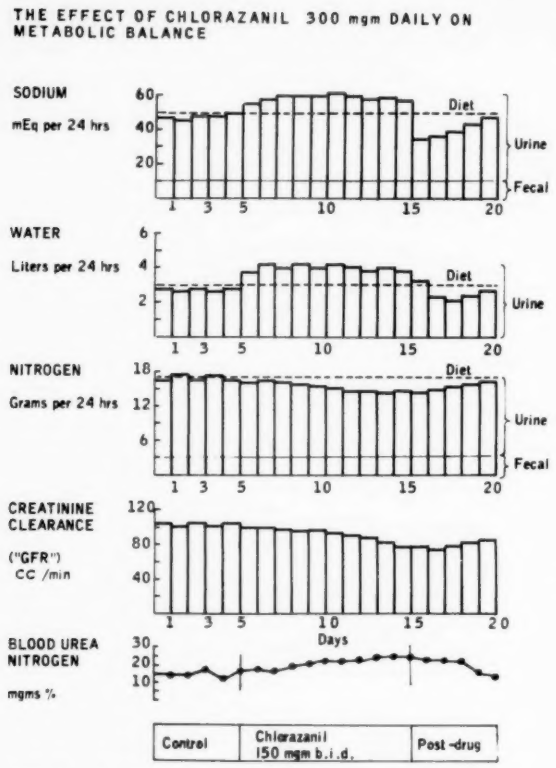

Fig. 8. Averages of data from two nonedematous hypertensive patients receiving 300 mg daily of chlorazanil. There is a progressive slightly negative sodium and water balance, and a slightly positive nitrogen balance, contemporary with a small depression of creatinine clearance and elevation of blood urea nitrogen concentration.

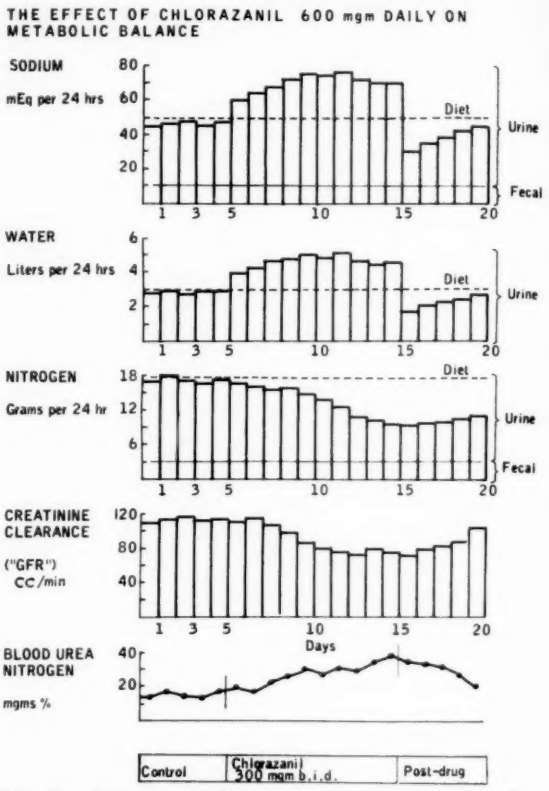

Fig. 9. Averages of data from two nonedematous hypertensive patients receiving 600 mg daily of chlorazanil. There is a greater magnitude of change in the balances described for Figure 8.

rise in blood urea nitrogen concentration and eleven a rise in plasma creatinine concentration after receiving chlorazanil, 150 mg b.i.d., for three weeks. Increases in both measurements were present in six of the twenty. The maximum blood urea nitrogen concentration detected was 38 mg%. Depressions of the endogenous creatinine clearances and 15-minute PSP excretions were found in some of the patients. The results of the urinalysis were not significantly affected by Daquin therapy; erythrocytes were never found. Decreases in body weight were not statistically significant in these nonedematous patients (Table X).

Discussion

The development of triazine derivatives as diuretic agents has been somewhat similar to that of the carbonic anhydrase inhibitors. After sulfanilamide was found to have diuretic

TABLE X

RENAL EFFECT OF THREE-WEEKS CONTINUOUS THERAPY WITH CHLORAZANIL 150 MGM. TWICE DAILY

Patient	B.U.N.		Plasma Creatinine		Creatinine Clearance		PSP.		Urinalysis	
	C	D	C	D	C	D	C	D	C	D
1.	19	18	.6	1.7	96	66	15	12	N	*F
2.	18	28	.9	1.5	100	52	25	10	*	*F
3.	23	33	.7	1.2	100	60	25	12	*	*F
4.	27	33	.5	1.0	85	60	20	14	*	*
5.	24	33	.7	1.1	90	63	22	12	*	*
6.	18	38	.8	1.3	105	72	25	14	N	F
7.	12	26	1.2	1.9	110	82	19	13	N	F
8.	10	21	.7	1.3	102	72	25	15	N	F
9.	13	15	.8	.7	101	102	25	25	N	F
10.	22	34	1.1	1.3	82	78	15	10	*	*
11.	22	20	.8	1.9	80	55	15	8	N	N
12.	14	9	1.2	1.2	102	104	25	25	N	N
13.	13	12	.9	.9	101	99	25	22	N	N
14.	14	11	.9	.8	99	101	25	25	N	F
15.	18	22	1.0	1.4	90	78	20	14	N	*F
16.	9	12	1.0	1.2	102	92	25	20	N	N
17.	30	21	1.3	1.1	65	68	10	10	N	F
18.	12	13	.9	1.1	102	101	25	25	N	F
19.	10	14	.8	1.0	104	85	25	15	N	N
20.	21	19	.9	1.3	82	72	20	17	N	N
Average	17	22	.9	1.2	95	78	22	16		

* Albuminuria (never more than 1+)

C = Control. D = After three weeks therapy. F = Cells (never more than 10 WBC/hpf). N = Normal.

properties, many years elapsed before the development of sulfonamide derivatives which were diuretic but relatively devoid of the serious toxicity of the first compound. In 1943 and 1944, Lipschitz and co-workers[1,10] showed that substances characterized chemically by

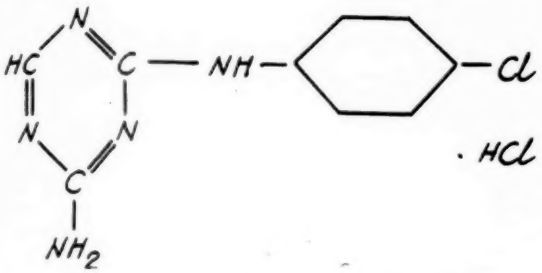

Fig. 10. Structural formula of chlorazanil.

the presence in the molecule of N=C—N groups possessed diuretic effects. The best known of these substances is 2,4 diamino-1,3,5-triazine or formoguanamine but it was not useful therapeutically because of its severe toxicity. The exploration of various triazine derivatives has culminated in the presentation of chlorazanil (Daquin) which is chemically 2-p-chloranilino-4-amino-1,3,5-triazine (Orpidan or Neo-Urofort) (Fig. 10) as an orally effective diuretic agent without serious toxicity.[11]

Hungarian workers reported alterations in renal tubular reabsorption of water with a lesser and independent effect on sodium and chloride excretion.[12] In Germany, studies[13] at somewhat low dosages (2 mg/kg) showed that the drug produced an increased excretion of sodium, chloride, and bicarbonate while the urinary excretion of potassium, ammonia, titratable acidity, and phosphate, as well as the pH, were not markedly changed. These changes were not associated with serum electrolyte alterations.

The results of the present study are in general agreement with the German as well as the Hungarian workers (who proposed to disagree with each other on basic mechanisms). In dogs, our results indicate that following the intravenous administration of chlorazanil there is a significant increase in sodium and water excretion. The percentile increase in water excretion is greater than with comparably potent natriuretic agents.

In man, the effective dose range is between 300 and 600 mg daily. Daquin shows an onset of action within two hours following oral administration and a duration of action of approximately 18 hours. Thus, it should probably be given once or twice daily if continued diuresis is desired. There is a definite effect in human beings on the excretion of sodium, so that it has been calculated to have a potency of 0.5, i.e., it is roughly one-half as

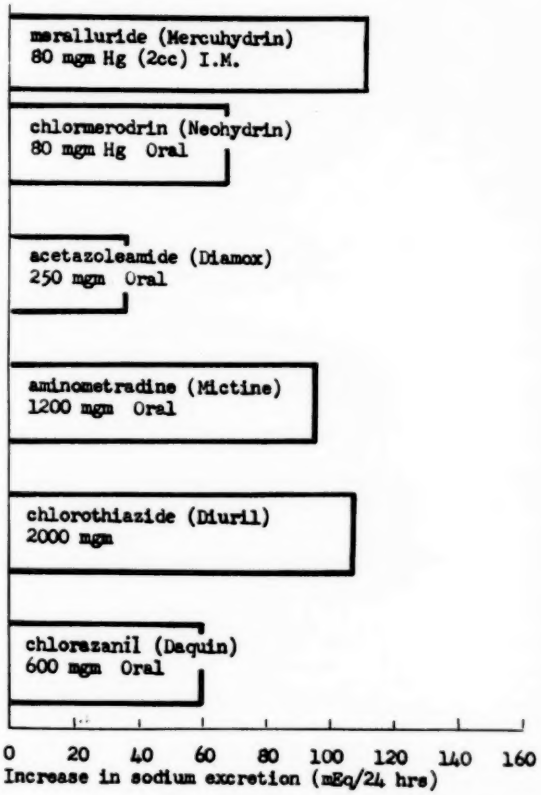

Fig. 11. Comparative potency of various natriuretic agents.

potent as meralluride (Mercuhydrin). Expressed somewhat differently, 1 ml of meralluride (Mercuhydrin) intramuscularly produces an increase in sodium excretion equivalent to that observed following the oral administration of approximately 600 mg of chlorazanil. Comparison with other orally active diuretic agents (Fig. 11) indicates that it is more potent than acetazolamide (Diamox), equipotent to chloromerodrin (Neohydrin), but less potent than aminometradine (Mictine) and chlorothiazide

(Diuril), when each is given orally as a single dose. However, patients rapidly develop tolerance to acetazolamide and to aminometradine, the clinical use of which, therefore, is sharply limited. If calculation of diuretic potency is based on urine volume changes (acutely) chlorazanil is more potent orally than is meralluride parenterally administered. Orally administered aminophylline had no effect upon the potency of concurrently administered Daquin.

Chronic daily administration is moderately and continuously effective, but is associated with laboratory evidence (elevated blood urea nitrogen and plasma creatinine with depression of creatinine clearance, PSP excretion, and positive nitrogen balance) of a decrease in glomerular filtration rate. This decrease is seen more rarely and then only to a minor degree when the daily dose is only 300 mg. There appears to be wide variation among patients in the effect of Daquin upon the measurements reflecting the glomerular filtration rate so that some patients can be treated indefinitely with this drug without the production of any change.

Concerning the mechanism of action of chlorazanil, the results of experiments to illustrate the electrolyte excretion patterns may be helpful. There is consistent and extensive augmentation of the excretion of sodium which is not completely paralleled by chloride. The excretion of bicarbonate is also enhanced, the order of magnitude is roughly $^1/_{10}$ to $^1/_4$ of that of chloride and this effect is not consistently observed. Urinary pH is slightly increased while titratable acidity, phosphate, and ammonia excretion are slightly depressed during the peak of drug action. Thus it appears that multiple mechanisms are affected by this drug or that a sole mechanism affected is different from those affected by carbonic anhydrase inhibitors or organomercurials. However, similar patterns of excretion have been observed following chlorothiazide administration except for the effect of the latter on potassium excretion not seen with chlorazanil.

Conclusions

Chlorazanil, when orally administered in doses of 300 or 600 mg/day, is an effective nonmercurial diuretic and a moderately effective natriuretic agent.

The chronic oral administration of chlorazanil, especially in doses greater than 300 mg daily, produced in some patients laboratory evidence of a fall in glomerular filtration rate.

The mechanism of action of this diuretic as reflected in its pattern of electrolyte excretion is different from those of mercurials, carbonic anhydrase inhibitors, and chlorothiazide. The most notable characteristic of chlorazanil is its proportionately greater effect on water excretion as compared to sodium excretion.

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Water Diuresis with Minimal Electrolyte Disturbances

Clinical Experiences with a New Triazine Compound Alone and Combined with a Carbonic Anhydrase Inhibitor*

IRVING HIRSHLEIFER, M.D., F.A.C.C.

Woodmere, New York

ELECTROLYTE displacements leading to disturbances in acid-base metabolism are primarily responsible for the lack of response to diuretic therapy administered vigorously or for prolonged periods. Although adjustment of water and electrolyte levels may be achieved through different mechanisms of action by selection from one of several classes of diuretic drugs, maintenance of electrolyte balance with continued use of any of these is likely to become a serious problem. Failure of diuresis in such instances compels re-establishment of biochemical equilibrium through the institution of "rest periods" or administration of the necessary electrolyte. Frequently, use of another type of diuretic will carry the patient until sensitivity to the original agent is restored. In practice, diuretic therapy is a complex affair requiring meticulous supervision and a realistic awareness of the limitations of the several drugs in current favor.

A rational approach to correcting deficiencies in available diuretic compounds involves the synthesis of new agents or of compounds related to existing drugs. In keeping with this concept, a number of triazine compounds have been prepared as oral diuretics. The properties and potency of 2,4-diamino-symtriazine (formoguanamine) have been appreciated since 1944.[1] Favorable reports of the activity of this material were published by Lipschitz and Stokey[2] in 1948 and by Turchetti[3] in 1950. Characterizing a chemically related triazine compound, chlorazanil, Ford stated that given orally this agent augmented sodium and chloride excretion.[4] Because the total solute was less than that observed with natriuretic agents of comparable potency, however, a primary effect on water excretion was suggested.

Recently, when a new triazine compound, 2-amino-4-anilino-1,3,5-triazine hydrochloride† (amanozine hydrochloride), identified in this paper as W-1191-2, was developed it was considered worthy of appraisal for diuretic efficacy. A second oral preparation, W-1753-1,† combining the triazine W-1191-2 with the carbonic anhydrase inhibitor, sulocarbilate, was also evaluated in the course of this study. Ford,[4] in discussing the pharmacodynamics of diuretic agents, indicated that carbonic anhydrase inhibitors augment the excretion of sodium, potassium, and bicarbonate but exert no apparent effect on excretion of chloride. On the other hand, triazines augment sodium and chloride excretion, while the excretion rate of potassium is only one-half that of sodium. This differ-

* From Division I, Medical Service and the Cardiac Clinic, Kings County Hospital Center, Brooklyn, New York.

† W-1191-2 and W-1753-1 were supplied through the courtesy of Warner-Chilcott Laboratories, Morris Plains, N. J.

TABLE I

Diuretic Activity of W-1191-2 and W-1753-1 Compared with Meralluride in the Dog

Drug	Dose	Total diuretic effect		
		Volume (cc)	Chloride (mg)	Sodium (mg)
W-1191-2	20 mg/kg, p.o.	204	312	298
W-1191-2 + W-1548 (W-1753-1)	20 mg/kg, p.o. 100 mg/kg, p.o.	330	380	510
Meralluride	0.029 ml/kg, i.v.	210	1197	488
	0.058 ml/kg, i.v.	395	1931	1741

ence in electrolyte excretion patterns suggests different mechanisms of action for the two agents. Moreover, it suggests the possible utilization of the compounds synergistically for a more potent and prolonged diuretic action without too great a change in electrolyte balance to eventually nullify the effect of the carbonic anhydrase inhibitor.

The concept of a synergistic action through a compound diuretic encouraged the preparation of W-1753-1 tablets containing 50 mg of W-1191-2 and 500 mg of sulocarbilate, formerly identified as W-1548.[5] The findings presented here are based on experiences with W-1191-2 and W-1753-1 in the treatment of abnormal water retention.

Pharmacology and Toxicology

W-1753-1 is a physical mixture of W-1191-2 and W-1548, each tablet containing 50 mg of the former and 500 mg of the latter drug. W-1191-2 is 2-amino-4-anilino-1,3,4,-triazine hydrochloride, a derivative of formoguanamine. W-1548 is *p*-sulfamyl-2-hydroxyethyl-carbanilate, a carbonic anhydrase inhibitor possessing an action similar to that of acetazolamide.[5] Table I demonstrates the diuretic activity (excess over control values in each parameter) of W-1191-2 alone and in combination with W-1548 in the dog, as compared with meralluride injection U.S.P. in doses equivalent in a 70 kg man to 2 ml and 4 ml of the commercially available solution. Each datum represents the average for five dogs. Neither drug exhibits other significant gross pharmacologic effects except for emesis which may occur with W-1191-2 at doses above 20 mg per kg orally.

TABLE II

Distribution of Treated Cases

Diagnosis	No. given W-1191-2	No. given W-1753-1
Hypertensive cardiovascular disease	5	7
Arteriosclerotic heart disease	8	6
Combination of both diseases	1	0
Rheumatic heart disease	3	4
Cor pulmonale	1	0
Premenstrual edema	1	0
Laennec's cirrhosis	0	2
Edema of unknown etiology	0	1
Total	19	20

Toxicity studies of W-1548 in rats and dogs at oral dosage of 50, 100, and 200 mg/kg/day for 12 weeks revealed no pathologic changes except crystalluria in dogs at all doses after the seventh week. A six-month chronic-toxicity study of W-1191-2 in rats at daily oral doses of 38, 74, and 114 mg per kg disclosed moderate kidney damage at the low dose and severe damage at the two higher doses. At the two higher dose levels, proteinaceous crystalluria was seen in the distal tubules.[6]

A six-month toxicity study using equal amounts of W-1191-2 and W-1548 was carried out in rats and dogs. Daily dose levels were 5, 10, 38, 76, and 114 mg per kg of each drug. Nephrotoxicity was observed at the three higher dose levels but not at 5 and 10 mg/kg/day. In other respects, the study disclosed no toxicity, and it would thus appear that a daily dose of W-1191-2 of at least 10 mg per kg or 700 mg in a 70 kg man should be safe for clinical use.[6]

Method

Patients for this study were selected from the cardiac clinic and medical wards, Division I,

TABLE III

Comparative Results of Therapy with W-1191-2 and W-1753-1

Previous medication	No. patients	Results of therapy			Side effects	
		Result	W-1191-2	W-1753-1	W-1191-2[a]	W-1753-1[b]
Digitalis	34	Excellent	6 (31.6%)	16 (80.0%)	Dizziness	Paresthesia
Meralluride	28	Improved	7 (36.8%)	2 (10.0%)	Lassitude	Weakness
Acetazolamide	4	Poor	6 (31.6%)	2 (10.0%)		Anorexia
Sulocarbilate	5		19	20		Hematemesis Melena
Chlorothiazide	3					
Low salt diet	4					

[a] Side effects in 1 case; drug discontinued.

[b] Side effects in 3 cases; drug discontinued in 2 patients with circumoral and extremity paresthesia in one instance, and hematemesis and melena in the second.

Kings County Hospital Center, as well as from private practice. All of the 39 patients treated showed frank evidence of water retention, referable to cardiac disease in 35 instances, to Laennec's cirrhosis in 2, to premenstrual tension in 1, and of unknown etiology in 1 case (Table II). Of this series, 19 patients were given the triazine compound W-1191-2 alone, and 20 received the compound diuretic, W-1753-1.

Of the 19 patients treated with W-1191-2, 14 required meralluride in addition to digitalis to maintain a compensated state. All but one were cardiac patients. W-1191-2 was administered in doses of 50 mg twice a day to 18 in the group and in doses of 100 mg twice a day to 1 individual. The treatment period extended from one week to as long as six months. The comparative clinical response to the new agent was determined by recording changes in weight and meralluride requirements and comparing them with the basic weight record and pretreatment parenteral mercury requirements. Although meralluride is given parenterally, it remains the yardstick of potency and dependability against which newly developed diuretic drugs are measured.

A group of 20 patients requiring diuretic therapy in addition to other measures for maintenance of satisfactory fluid balance were given W-1753-1. Initially, the drug was administered in doses of 2 tablets twice daily, representing 100 mg W-1191-2 and 1000 mg sulocarbilate twice a day. With continued usage, however, it was found that adequate diuresis could be achieved with an intermittent schedule of 2 tablets twice daily on alternate days or, in some instances, three times weekly. Aside from the cardiac cases two patients with Laennec's cirrhosis and one with edema of unknown etiology were treated with W-1753-1 in this series. As before, the treatment period ranged from one week to six months, and efficacy of the diuretic was determined on the basis of changes in weight and meralluride requirements.

A further breakdown of the clinical group indicates that 5 females and 14 males, ranging in age from 27 to 81 years, were treated with the new triazine diuretic. W-1753-1 was administered to 11 females and 9 males, 38 to 74 years of age. On the whole, these patients were representative of the types encountered in a cardiac clinic or by the practicing cardiologist.

Results

The results achieved with both diuretic agents are presented in Table III. Absence of edema, as determined by weight changes and by the degree of success in achieving "dry weight," was considered in appraising the efficacy of the medication. When the patient was converted from decompensation to a compensated state, or if either diuretic could be substituted for meral-

TABLE IV

Effect of Continuous Therapy with W-1753-1 on Serum Electrolyte Levels in Four Patients

Patient and age	Time of determination	Sodium (meq/L)	Potassium (meq/L)	Chloride (meq/L)
Female, 43	Start of therapy	134	4.9	106
	6 days of therapy	140	5.1	98
	27 days of therapy	142	4.8	105
Male, 55	Start of therapy	130	3.7	117
	5 wk of therapy	138	4.3	108
Female, 67	Start of therapy	141	4.4	110
	4 mo of therapy	152	3.2	101
Male, 68	Start of therapy	152	3.2	101
	5 mo of therapy	142	4.3	104
	7 mo of therapy	—	4.9	103

luride and maintain adequate fluid balance, the result was termed "Excellent." When the state of compensation was improved, or the amount of meralluride necessary to maintain optimal fluid balance was reduced, the result was judged "Improved." All other findings were reported as "Poor" results.

Results with W-1191-2 (Amanozine Hydrochloride): With W-1191-2, the results were excellent in 6 (31.6 per cent) of the cases, improved in 7 (36.8 per cent), and poor in 6 (31.6 per cent). Of the 6 patients showing a poor response, 4 were refractory to previous medication with digitalis preparations and meralluride. One individual with rheumatic heart disease developed dizziness and lassitude and the drug was discontinued. Laboratory examinations carried out during this study disclosed no changes in urinalysis, blood picture, or blood urea nitrogen ascribable to W-1191-2. From observation of this limited group of patients, it would appear that W-1191-2 is a relatively weak diuretic for clinical use although, in the dosage given, no obviously serious toxic effects occurred.

Results with W-1753-1(Amanozine Hydrochloride Plus Sulocarbilate): With the compound diuretic, W-1753-1, results were excellent in 16 (80 per cent) of the cases, improved in 2 (10 per cent), and poor in 2 (10 per cent). Where an excellent clinical response was achieved, all of the patients were able to dispense with meralluride therapy completely. Of greater satisfaction to both physician and patient was the superior state of fluid balance for which W-1753-1 was responsible. Two of the patients in this series, those with Laennec's cirrhosis, in whom meralluride therapy had failed, had previously been responsive only to paracentesis. The remaining 14 patients were cardiac cases.

Toxic and Side Effects: Although two patients showed improvement with W-1753-1, therapy was discontinued after two weeks. Melena and hematemesis appeared in one case. This patient had experienced similar episodes in the past as a result of hiatus hernia complications. In the second patient, circumoral and extremity paresthesia developed, although from the viewpoint of diuresis he did as well on W-1753-1 as on the chlorothiazide for which it was substituted. Of the two patients showing a poor response, one received the drug for only 24 hours, while the second had been subjected to treatment with virtually all available diuretics and had failed to respond. Postmortem examination revealed fluid in all serous cavities for which no etiology could be established.

None of the patients in this series developed signs of tolerance or unresponsiveness to W-1753-1 even after several months of continuous therapy. In some measure, this may be attributed to the maintenance of electrolyte balance through the combination of two diuretics with different excretion patterns. Evidence of negligible electrolyte disturbance may be seen in Table IV, where serum levels are presented for four patients on relatively long-term therapy.

Discussion

In a previous study, sulocarbilate, a carbonic anhydrase inhibitor, was found to produce excellent diuresis in 22.2 per cent of cases treated for abnormal water retention.[5] Results obtained during this study with a new triazine compound, W-1191-2, were excellent in 31.6 per cent of a similar group of cases. In contrast, a full 80 per cent of the patients treated with W-1753-1, a combination of the two drugs, showed an excellent response to medication. A synergistic action by these two types of diuretics is strongly suggested.

Of equal if not greater importance, W-1753-1 exerted a negligible effect on the serum electrolyte picture even when administered continuously over a period of several months. The absence of signs of progressive tolerance or complete lack of diuretic response may in part be attributed to insignificant disturbance of electrolyte excretion patterns. If the effect of the diuretic combination was purely additive, some degree of electrolyte imbalance might have been expected to appear sooner or later. The fact that W-1753-1 maintained its initial diuretic effect over relatively long treatment periods and electrolyte disturbances were not manifested is considered further evidence of a synergistic action between W-1191-2 and sulocarbilate.

Conclusions

W-1191-2, a new triazine compound, appears to offer a mild diuretic action in clinical use. No serious toxic effects have been observed with this agent administered for several months during the course of this study. W-1753-1, a combination of W-1191-2 and sulocarbilate, exhibits an enhanced and more prolonged diuretic action than either drug alone.

With W-1753-1, the development of tolerance and lack of response has not occurred even when the combined diuretic was administered continuously for several months. In addition, the serum electrolyte picture in patients treated with this diuretic for relatively long periods remained essentially unchanged. Consideration of the results in this present series indicates that W-1753-1 is a synergistic combination of two mild diuretic agents which together act as a potent diuretic and in a manner to cancel out electrolyte disturbances that might be anticipated with continued usage of either of these components alone.

Combinations of triazine derivatives and carbonic anhydrase inhibitors are worthy of further exploration in the field of diuretic therapy.

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Evaluation of Chlorothiazide in the Diuretic Therapy of Congestive Heart Failure*

LEON J. WARSHAW, M.D., F.A.C.C.

New York, New York

UNTIL RECENTLY, diuretic agents were usually administered to patients with congestive heart failure only when digitalization—often to the point of toxicity—sedatives, and restriction of activity had failed to restore compensation. The indication for their use was the persistence of such obvious manifestations of failure as rales at the lung bases or dependent edema, and their efficiency was measured by the increase in urinary output. The demonstration of the role of sodium retention in congestive failure led to the abandonment of the restriction of fluid intake in favor of decreasing the salt content of the diet. This noteworthy advance had but little effect on the manner in which diuretics were employed.

In a study published from this clinic ten years ago,[1] a regimen for the routine treatment of congestive heart failure based on the daily use of a mercurial diuretic was proposed. It was shown to permit 90 per cent of hospital patients (instead of the usual 50 to 60 per cent) to be discharged free of failure, and to shorten their hospital stay from the usual three to four weeks to an average of about one week. The fundamental principles of this method were: (1) The frequent use of a mercurial diuretic, daily at first, to achieve a steady and continuous diuresis until the patient was entirely free of the accumulated excess extracellular fluid; (2) sole reliance on the meticulously recorded weight of the patient as a guide to adjusting the frequency and magnitude of the diuretic doses; (3) continuation of the regimen adjusted to meet the minimal requirements of the individual patient in order to maintain compensation. Once compensation was restored, some patients were able to carry on satisfactorily with mercurial injections at intervals of a week or longer; others required two or three injections a week, and a small number continued to require a daily injection.

The inconvenience of frequent injections over a period of years has stimulated interest in the development of new diuretic drugs that might be used orally.[2,3] Several have demonstrated a diuretic potency sufficient to provide adequate maintenance of some patients, usually those with milder degrees of failure. Their usefulness has been limited, however, by the gastrointestinal irritation caused by doses required for the diuretic effects desired in most patients, or by their loss of potency on continued administration.

The introduction of chlorothiazide,† a heterocyclic acid related in structure to the carbonic anhydrase inhibitors, has been hailed as a solution to these problems. Labeled the "most potent oral diuretic available at the present time,"[4] this drug has been shown to be effective in all types of fluid retention[5] including those associated with renal insufficiency.[6] Except for the tendency to produce hypokalemia which merely reflects its diuretic potency, its use has not been accompanied by significant untoward reactions or evidence of toxicity.[7] This paper is a report of one year's clinical experience with the use of this drug in patients with heart failure of varying etiology and also in a smaller group of noncardiac patients with fluid retention secondary to endocrine imbalance.

* From the Cardiovascular Research Unit, Beth Israel Hospital, New York City, and the Medical Departments of Paramount Pictures Corporation and United Artists Corporation, New York City.

† Supplied as Diuril by John R. Beem, M.D., Merck Sharp & Dohme, West Point, Pennsylvania.

Method

Except for 17 cases with acute decompensation, all of the patients were treated on an outpatient basis. Diet and other medications were prescribed as indicated, but every effort was made to keep these factors constant during the period of observation. Except for those cases in which satisfactory diuresis was not produced by the chlorothiazide, no other diuretic agents were administered.

No attempt was made to standardize the dose of chlorothiazide. In most cases, a single oral dose of 1.0 g was given each morning. Many of the patients were found to require a second dose of 1.0 g in mid-afternoon. In three cases which seemed resistant, increased doses up to 4.0 g/day for several days were tried, but proved to be no more effective, and the chlorothiazide was abandoned in favor of other forms of diuretic therapy.

In the cases responding satisfactorily, the dose was lowered to 0.5 g and/or the interval between doses increased progressively until the minimum amount of the drug needed for optimal maintenance of each patient could be established. Patients receiving prolonged continuous chlorothiazide therapy were given potassium supplements in amounts that did not appear to influence the diuresis.

A diary was kept for each patient in which was entered the body weight (determined on the same scale in the identical state of dress and at the same time each day) together with the kind and amount of medication taken and a description of variations in signs or symptoms. Except for those in the hospital or receiving professional nursing care in the home, each patient kept his own records. Patients were examined regularly throughout the period of observation at intervals ranging from once a day to once every two or three weeks depending upon their clinical condition and its rate of change.* On each visit, the diary was reviewed with the patient to assure the reasonable accuracy of the record and to discuss any entries that were not entirely clear. Laboratory tests were performed as indicated by the patient's condition and course.

There were 18 patients, not included in Table I, who were dropped from the study because of deviations from the prescribed regimen or failure to keep a satisfactory diary.

The wide variation in kind and severity of case, in the size and frequency of chlorothiazide doses, and the lack of proper control observations obviously make any statistical analysis of the results impossible. Accordingly, cases were simply classified as "satisfactory" when chlorothiazide alone produced the desired diuretic response, and "unsatisfactory" when other diuretic agents were required or the chlorothiazide was not well tolerated.

* The author wishes to express his appreciation to the physicians and nurses, too numerous to be listed individually, who assisted in the observation and treatment of the patients with such care and diligence.

Results

Chlorothiazide was administered to 98 adults with clinical evidence of fluid retention amenable to diuretic therapy (Table I). They were divided into three groups:

(1) (a) Cases of acute congestive heart failure representing either an initial bout of decompensation or a relapse following abandonment of a maintenance regimen (17 cases).

(b) Cases requiring diuretics as part of a regimen to maintain an optimal level of cardiac compensation (44 cases).

(2) Cardiac cases in which symptoms and signs of congestive failure were produced by endocrine-induced sodium and fluid retention (13 cases).

(3) Cases of endocrine-induced fluid retention with no evidence of heart disease (24 cases).

Most of the cardiac cases had arteriosclerotic and/or hypertensive heart disease. The remainder were of either congenital or rheumatic etiology. Patients with rheumatic activity or acute myocardial infarction were excluded, as were patients with edema due to cirrhosis, nephrosis, chronic renal failure, and peripheral vascular disease. Patients under treatment with hypotensive agents were also excluded.

Acute Congestive Failure

Chlorothiazide was given to 17 patients with acute congestive failure of a moderate or severe degree. In each case physical activity was markedly restricted. The dietary intake of sodium was limited to less than 1.0 g/day and the fluid intake maintained in excess of 2,000 cc daily. All but two patients were digitalized and maintenance doses of a digitalis preparation were continued.

"*Satisfactory*" *Response:* Chlorothiazide proved to be a "satisfactory" diuretic in 13 (76 per cent) of the patients who responded in a manner comparable to those successfully treated by Gold *et al.*[1] with the regimen based on the daily mercurial injection. The following case demonstrates a typical response:

Case 1. A male, age 62, had hypertensive and arteriosclerotic disease (Fig. 1). One previous bout of congestive failure had occurred one year ago. Three months ago he stopped all medication. Gradually he developed dyspnea on effort, orthopnea, ankle edema,

and paroxysmal nocturnal dyspnea. On admission, he had engorged neck veins, congested lungs with small bilateral hydrothorax, engorged liver and edema to the upper thigh level. Blood pressure was 210/136.

He was treated with salt-poor diet, digitoxin, rest, and chlorothiazide 1.0 g b.i.d. By the fifth day, he was virtually free of symptoms after losing 15 lb of edema fluid. The blood pressure fell to 190/106. However, the regimen was maintained and over the next 15 days, he gradually lost another 15 pounds. Blood pressure was 170/102. The patient was discharged fully compensated on the 25th day, with a blood pressure of 160/96.

The following case illustrates the antidiuretic effect of ascites attributed to the inhibition of renal blood flow by the increased abdominal pressure, and a return of responsiveness to chlorothiazide following paracentesis:

CASE 2. A female, age 79, with evidence of arteriosclerotic heart disease with "burned-out hypertension" following old myocardial infarction, bundle branch block, and hyperthyroidism (Fig. 2). Chronic severe congestive heart failure had been present for about 15 years, requiring intensive diuretic therapy for maintenance, with several bouts of severe failure accompanied by ascites and hydrothorax, the most recent two years ago. Occult hyperthyroidism was discovered and treated by therapeutic doses of radioactive iodine three years ago. Radioiodine studies six months ago reported euthyroid levels.

This woman developed tissue sensitivity to mercurials so that each injection produced a painful lump. Inflammation at the site of injection resulted in irregularity of absorption and uncertain diuretic response. For this reason the patient was maintained on oral medication. After many trials of various combinations, optimal results were obtained on a regimen consisting of ammonium chloride 6.0 g daily in divided doses, chlormerodrin (Neohydrin) 6 tablets a day alternating with acetazolamide (Diamox) 0.5 g/day. Digitoxin 0.1 mg was continued throughout. Dietary intake of sodium was limited to about 1.0 g/day and fluids were allowed as desired.

On the above regimen the patient was fairly well maintained for a period of about six months. Without any significant precipitating incident or cause, a gradual weight gain of about 9 lb over a period of about four weeks was noted, accompanied by a gradual increase in the symptoms of failure. As indicated in Figure 2, chlorothiazide 1.0 g/day was substituted for the acetazolamide given every other day. The chlormerodrin was continued. The weight curve continued to rise and it became apparent that most of the additional excess extracellular fluid was going into the abdomen to form ascites. Since this patient was greatly upset by the prospect of another paracentesis, it was decided to attempt to control the ascites by intensifying the diuretic therapy. Chlorothiazide dose was increased to 2.0 g/day

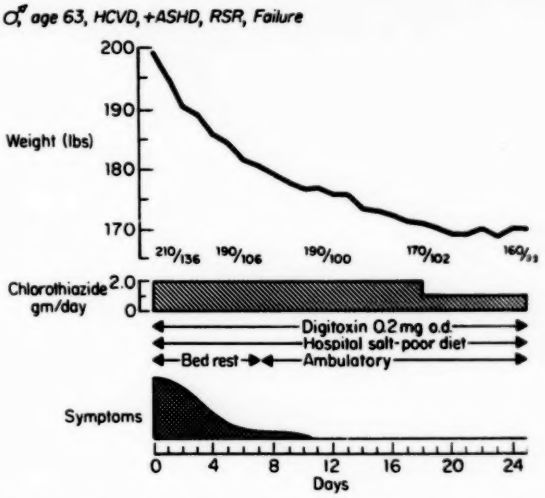

Fig. 1. Case 1. Chlorothiazide as a diuretic in the treatment of acute congestive failure. (HCVD = hypertensive cardiovascular disease; ASHD = arteriosclerotic heart disease; RSR = regular sinus rhythm.)

with no effect on the rising weight curve. After nine days, chlorothiazide was increased to 3.0 g/day and daily meralluride (Mercuhydrin) 2 cc intramuscularly was substituted for the chlormerodrin tablets. After one week, chlorothiazide was increased to 4.0 g/day, while the mercurial injections and the ammonium chloride were continued. For two days, the meralluride was given twice daily. Blood electrolyte studies showed only a mildly depressed chloride level. Because of increasing discomfort, the patient was admitted to the hospital, where an abdominal paracentesis was done, resulting in a weight loss of 15 lb.

Following the paracentesis, all diuretic drugs were discontinued except for chlorothiazide 1.0 g/day. A progressive diuresis was noted with gradual loss of almost 20 lb over the next eight days. By the fourth day after paracentesis, the patient's symptoms had declined so that she was reasonably comfortable at rest and became dyspneic only after moderate activity. The patient was maintained on the chlorothiazide and digitoxin and was discharged from the hospital on the 20th day following the paracentesis. About a week after her discharge from the hospital, it was necessary to increase the chlorothiazide dose to 2.0 g/day, presumably in order to compensate for the increased sodium content of the home diet as compared to the diet prepared in the hospital. On this level of dosage, she remained fairly well controlled for approximately two months, when she expired suddenly in what apparently was another episode of myocardial infarction.

"*Unsatisfactory*" *Response:* Four patients with acute congestive failure were classified as "unsatisfactory:"

CASE 3. A female, age 58, had hypertensive and

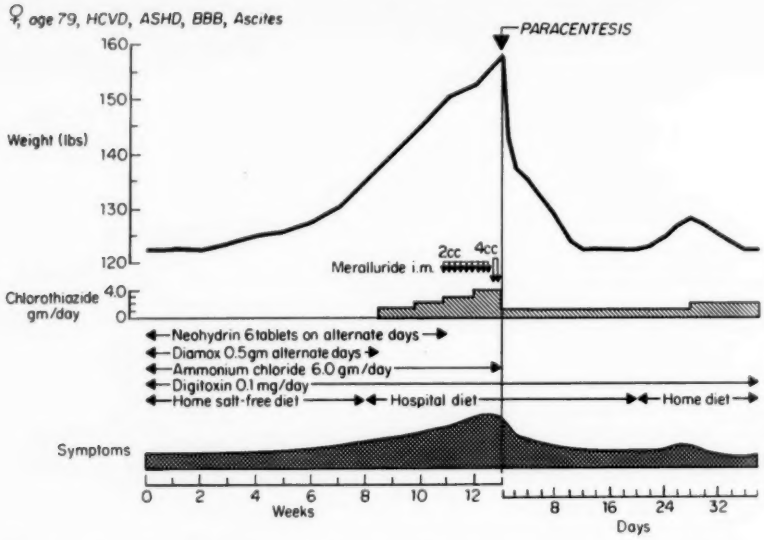

Fig. 2. Case 2. Resistance to intensive diuretic therapy in a patient with ascites due to congestive heart failure and response to chlorothiazide following abdominal paracentesis (BBB = bundle branch block).

arteriosclerotic heart disease, auricular fibrillation, and diabetes mellitus. A highly neurotic individual given to unreasonable and inconsistent reactions, she developed nausea and vomited almost immediately after each dose of chlorothiazide. Since she had demonstrated in the past similar reactions to a variety of usually well-tolerated oral preparations, including a placebo, and on this occasion had been heard to declare "The pills will make me sick—only the injections for the water will help," it was felt that the reaction was either consciously or unconsciously self-induced rather than a reflection of the irritant effects of chlorothiazide on the gastrointestinal tract.

Case 4. A male, age 67, had arteriosclerotic heart disease and several old myocardial infarctions. He was critically ill on admission with severe pulmonary congestion and anasarca. He lost 8 lb on the first two days of treatment although there was no obvious diminution in the clinical signs of congestion and episodes of pulmonary edema continued. Fortunately, these responded to bloodless phlebotomy, oxygen by positive pressure mask, and morphine. When, during the next 36 hours, four doses, each of 1.0 g of chlorothiazide, failed to produce any further loss of weight, 2 cc of meralluride was injected intramuscularly. A large diuresis ensued, resulting in the loss of 7 lb in 24 hours. Daily injection of the mercurial continued the diuresis, until all of the excess extracellular fluid had been eliminated. The patient's condition improved dramatically and by the time he reached "dry weight" on the 14th day, all of the symptoms had cleared, except for persistent fatigue and weakness. It is worthy of note that at this time his serum sodium and potassium levels were within normal limits and the serum chloride level, although somewhat depressed, was not low enough to be indicted as the cause of the residual symptoms. However, they cleared gradually after an additional week of rest and improvement in his appetite and food intake.

Case 5. A male, age 61, had hypertensive and arteriosclerotic heart disease. He was digitalized five years before after a myocardial infarction had precipitated congestive failure. There was a six months' history of slowly progressive dyspnea on effort, orthopnea, epigastric fullness, and ankle edema, and he had gained about 20 lb. He was allowed to be ambulatory. Daily maintenance dose of digitoxin 0.2 mg was continued and sodium restriction was intensified.

Chlorothiazide 1.0 g daily produced gradual weight loss of 5 lb in seven days. Increasing the dose to 2.0 g, to 3.0 g, and finally to 4.0 g/day over the next eight days produced only an additional loss of 2 lb. The blood count remained normal. On 2.0 g twice a day, the patient complained of anorexia and vague epigastric discomfort. Change to a daily mercurial injection produced prompt diuresis with return to "dry weight" in six days.

Case 6. A male, age 38, had rheumatic heart disease with mitral stenosis and insufficiency, aortic insufficiency, regular sinus rhythm. Rheumatic fever had occurred at the age of 9, again at 13. Increasing dyspnea and palpitation on effort, paroxysmal nocturnal dyspnea, and nocturnal ankle edema were present for about two months following an attack of "influenza."

He was treated with low salt diet and chlorothiazide 1.0 g b.i.d. alone for five days. He lost 2 lb on the first day, but regained it by the third day and weight remained the same. On the sixth day, 2 cc of Mercuhydrin produced a weight loss of 3 lb. On daily mercurial injections, he continued to lose weight. On the 13th day he had lost 13 lb and was free of signs and symptoms.

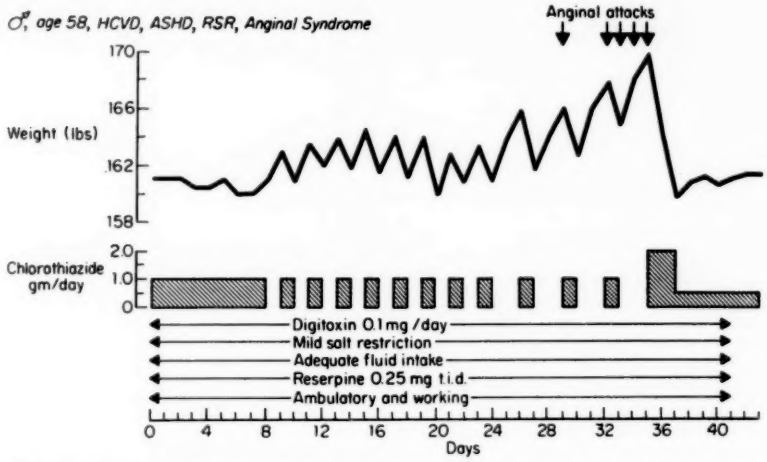

Fig. 3. Case 7. Adjustment of maintenance doses of chlorothiazide in a patient with anginal syndrome as a manifestation of early congestive failure.

Weight remained constant despite discontinuation of mercurial injections. The patient was digitalized and discharged on maintenance dose of digitoxin.

REGIMEN TO MAINTAIN CARDIAC COMPENSATION

Chlorothiazide was given to 44 patients who required continuous diuretic therapy to maintain cardiac compensation. Included in this group were 12 of the 13 cases who had a satisfactory response to chlorothiazide when in acute failure. Their regimen was continued without change.

The remainder of this group had been maintained on digitalis, a reduced salt intake, and injections of mercurial diuretics ranging from 0.5 cc to 2 cc in dose and from daily to once every ten days in frequency. Most required two or more injections per week in order to maintain a weight at which their capacity for activity was maximal and their signs and symptoms of congestive failure either entirely absent or minimal. All had demonstrated satisfactory stability for at least four weeks prior to the period of observation. In most of this group the injections were stopped and, regardless of their frequency, replaced by a daily oral dose of chlorothiazide. In a few, the oral doses initially followed the same schedule used for the injections. If the patients demonstrated a tendency to gain weight, the size and/or the frequency of chlorothiazide doses was increased progressively until the weight increment had been lost and the previous stability had been restored. If no fluctuations in weight or symptoms were seen after a week or so of chlorothiazide doses, their frequency was diminished to every other day, then every third day, and so on. In this way, the minimal amount of treatment needed to maintain each patient was determined.

The following case demonstrates a typical result:

CASE 7. A male, age 58, had hypertensive and arteriosclerotic heart disease with an anginal syndrome (Fig. 3). He had known hypertension for about 15 years. For about two years, there were increasingly frequent episodes of substernal oppression and dyspnea, always following physical or emotional stress and responding promptly to nitroglycerin. He had been taking reserpine 0.25 mg t.i.d. for almost one year for the relief of headaches and to diminish emotional excitability, with good effect. After digitalization and reduction in salt intake and mercurial injections produced a loss of 12 lb of extracellular fluid (despite the absence of lung rales and detectable edema of the legs at the outset of therapy) he was stabilized on two injections per week of 1 cc of meralluride. Whenever these were omitted and his weight rose above 165 lb, the anginal attacks returned, only to disappear again when a diuresis brought his weight below that figure. At such times, no signs of fluid retention were detected, although the patient claimed he could see and feel some "puffiness" of his fingers and toes.

On a daily dose of 1.0 g of chlorothiazide, the patient's weight remained constant and he felt fine. Lowering the dose to 1.0 g every second day produced a fluctuating weight curve at a slightly higher level. The chlorothiazide doses produced a diuresis of from 2 to 4 lb, but this was promptly regained on the "drugless" day. The patient, however, continued his former well-being.

When the dose was lowered to 1.0 g every third day, the weight curve slowly rose. The chlorothiazide con-

TABLE I

Usefulness of Chlorothiazide as the Sole Diuretic Agent in the Treatment of Heart Failure and Endocrine Edema

	Total cases	"Satisfactory" response	"Unsatisfactory" response
Congestive Heart Failure			
Treatment to restore compensation	17	13	4
Maintenance regimen	44	39	5
Combined Endocrine and Heart Disease			
Heart disease and steroid therapy	5	3	2
Heart disease and estrogen therapy for prostatic cancer	3	3	0
Heart disease and premenstrual edema	2	2	0
Heart disease and pregnancy	3	3	0
Fluid Retention of Endocrine Etiology			
Premenstrual edema	19	18	1
Steroid therapy	4	4	0
Aldosteronism	1	0	1
Total	98	85	13

tinued to produce a satisfactory diuresis, but not enough to remove all of the fluid accumulated since the previous dose. After eight days on this regimen, his weight rose above the "threshold" level and the attacks of angina returned. The dose of chlorothiazide was increased to 1.0 g twice a day for two days, during which 10 lb were lost. It was thereafter maintained at 0.5 g daily. On this regimen the weight stayed below the "threshold" level and the patient remained asymptomatic. This had been maintained continuously without complication for five months at the time this report was prepared.

Although the dose schedule required did not appear to conform to that of the injected mercurials employed prior to the period of observation (this will be discussed subsequently), oral chlorothiazide appeared to be a perfectly satisfactory diuretic in 39 (89 per cent) of this group of 44 cases. Four patients, although originally well maintained on this new diuretic, appeared to acquire a tolerance to it. They had received chlorothiazide for 13 days, two weeks, 14 weeks, and 18 weeks, respectively, in doses of 1.0 g daily, 1.0 g twice a day, 0.5 g daily, and 1.0 g twice a day, respectively, when this occurred. The fifth "unsatisfactory" case had shown no initial response to chlorothiazide. All five demonstrated a good diuresis on the resumption of mercurial injections.

COMBINED ENDOCRINE AND HEART DISEASE

This group (Table I) consisted of 13 patients with either rheumatic or hypertensive and/or arteriosclerotic heart disease who were well compensated until a change in endocrine balance caused sufficient sodium and water retention to produce classical signs and symptoms of congestive failure. Hormone therapy was responsible for this syndrome in 8 cases—5 cases after prolonged corticosteroid administration and 3 cases after massive doses of estrogens for metastatic prostatic carcinoma.

The other cases were of endogenous origin. Two were rheumatic cardiacs whose cyclic premenstrual fluid retention was sufficient to cause mild but definite pulmonary congestion. The three patients with congestive heart failure occurring early in the middle trimester of pregnancy were placed in this group although their symptoms were probably caused less by the altered endocrine balance than by the physiologic increase in blood volume and cardiac output needed to satisfy the placental circulation.

Eleven of these 13 patients were treated satisfactorily by chlorothiazide variously administered to suit each patient's individual requirements. Two cases were judged "unsatisfactory:"

Case 8. A female, age 38, who had rheumatic heart disease with advanced rheumatoid arthritis was on continuous steroid therapy for over two years. Increase in steroid dosage because of a flare-up in joint symptoms was followed by a gradual weight gain and the onset of heart failure symptoms. Chlorothiazide 1.0 g b.i.d. produced a satisfactory diuresis but the patient complained of epigastric discomfort, substernal burning, and mild nausea following almost every dose. An organomercurial by injection was substituted for the chlorothiazide and provided adequate diuresis without side effects.

This patient was subsequently shown to have the active duodenal ulcer so often seen in patients receiving massive or prolonged corticosteroid therapy. No attempt was made to determine whether the symptoms noted after chlorothiazide ingestion represented an

inherent effect of this drug, irritation of an ulcer already then established, or simply coincidental episodes of peptic ulcer activity. Observation of a few instances of gastrointestinal irritation after chlorothiazide makes the first or second possibilities more likely than the third.

CASE 9. A female, age 69, had arteriosclerotic heart disease with generalized arteriosclerosis and senility, varicose veins, and osteoarthritis. A steroid-salicylate preparation originally given in intermittent courses to relieve arthralgias had been taken regularly for over six months in at least five and sometimes ten times the dose originally prescribed by her physician, whom she kept in ignorance of this self-treatment.

When first seen, there was massive edema of the extremities and lower trunk and moderate pulmonary congestion. Satisfactory salt restriction was virtually impossible to maintain, as the patient persistently disobeyed dietary instructions. Oral chlorothiazide was almost totally ineffective as a diuretic. With daily mercurial injections, the greater part of the excess fluid was gradually eliminated over a three-week period, at the end of which the patient was lost to follow-up.

ENDOCRINE-INDUCED FLUID RETENTION WITHOUT HEART DISEASE

Premenstrual Fluid Retention: Chlorothiazide was effective in preventing the fluid retention and minimizing the symptoms associated with the premenstrual period in 18 out of 19 cases. In each case the premenstrual period had almost invariably been associated with the gradual accumulation of from 4 to 8 lb of excess extracellular fluid, accompanied by engorgement of the breasts that was often painful, abdominal bloating, "nervousness," and emotional irritability and depression. In some, ankle edema was noted. Shortly after the onset of menstrual bleeding, a spontaneous diuresis occurred, bringing relief from these symptoms. In almost half the group, there was moderate to severe dysmenorrhea and three women complained of lethargy and fatigue during and for a few days following the menstrual flow. This pattern was repeated with almost every cycle. Although there was considerable variation from case to case, each individual displayed a remarkable uniformity of this recurrent syndrome in regard to both the amount of weight gained and the sequence of symptoms.

All of these women had found diuretic drugs supported by moderate restriction of sodium intake an effective method of preventing or aborting these episodes. Therapy was started 8 or 10 days prior to the expected onset of the next menstrual flow. Chlorothiazide 0.5 g daily was substituted for the previous diuretic. If the tendency to increase in body weight persisted, the chlorothiazide dose was doubled. Only two cases required as much as 2.0 g/day. When the weight remained constant, the dose was reduced to 0.25 g/day or to 0.5 g every other day. The latter schedule seemed to be more effective than the former in preventing the fluid retention.

Chlorothiazide was almost uniformly effective in preventing the premenstrual fluid retention in each of the 19 cases, all of whom were under observation for from four to eight months. As with the other diuretic preparations, this was accompanied by the virtual absence of the usual premenstrual symptoms and, usually, a marked reduction of the severity of the dysmenorrhea so frequently associated with the subsequent menstrual flow.

Only one case was judged to be "unsatisfactory:"

CASE 10. This was a female, age 29. Chlorothiazide 0.5 g/day was successful in inhibiting the fluid retention observed in previous periods. However, after several days of continuous chlorothiazide therapy, she developed feelings of weakness and slight dizziness coupled with an unpleasant sense of inner excitement and impending difficulty. This was repeated on three consecutive trials. These symptoms had not been associated with the use of acetazolamide (Diamox) or aminoisometradine (Rolicton) which proved equally effective in preventing the premenstrual fluid retention, nor were they inhibited by the administration of potassium chloride in conjunction with the chlorothiazide. Although she was under psychiatric treatment and previously had suffered mild anxiety attacks, this particular complex of symptoms had never been experienced prior to the chlorothiazide therapy.

The possibility that these symptoms reflected a purely coincidental emotional crisis was denied by the patient, who, at the time of observation, had acquired rather good insight into her emotional behavior. This was confirmed by her psychiatrist. Although there was no previous history of any drug sensitivity, this reaction would appear to fit best into the category of drug allergy or idiosyncrasy.

Edema Due to Steroid Therapy and Aldosteronism: Chlorothiazide was found to be effective in relieving and controlling mild to moderate fluid retention observed in 4 patients receiving steroid therapy for various forms of arthritis. It was also effective in one case of secondary aldosteronism in which fluid retention appeared to in-

itiate severe migraine attacks. However, continuous doses of 2.0 g/day for several weeks led to spells of profound weakness and fatigue. Serum electrolyte levels were found to be within the lower part of the normal range on two occasions but blood specimens were not drawn during one of these episodes. Finally, despite supplementary potassium chloride in doses up to 4.0 g/day, the patient experienced an episode of severe collapse which appeared to respond to intravenous saline with added potassium. Unfortunately, laboratory studies were not obtained on this occasion but it unquestionably was the result of prolonged and intensive sodium restriction and diuretic therapy.

Discussion

In the study of a new drug, the pharmacologist attempts to assess its mechanism and speed of action, potency, toxicity, route and speed of elimination, etc., by a series of carefully controlled experiments. The clinician, on the other hand, is usually more concerned with the usefulness of the drug in a particular disease or syndrome and, frequently, in a particular patient. His tendency to be interested primarily in the results of treatment with the drug rather than in the critical analysis of how these were obtained is probably responsible for the overenthusiastic acclaim that often heralds new preparations. In many instances, the benefits originally attributed to a particular drug have proved instead to be derived from the closer observation of the patients treated with it and better management of other elements in the regimen of treatment. It seems advisable, therefore, first to define the use of diuretics in the treatment of congestive heart failure and then to assess the usefulness of chlorothiazide in this role.

DIURETIC THERAPY IN CONGESTIVE FAILURE

Whenever possible, the clinician attempts to correct the cause of heart failure by measures such as improving cardiac output with digitalis, restoring normal cardiac rhythm with quinidine or procain amide, treating infection with antibiotics, reducing fever with antipyretics, etc. Often, however, these are inadequate or too slow. In addition to producing discomfort and distress, the accumulation of excess extracellular fluid imposes a physiologic burden that, in itself, can produce further cardiac impairment, thus establishing a vicious cycle. Consequently, unnecessary delay in employing diuretics is inexcusable and often dangerous.

The goal of diuretic therapy is the removal of the excess extracellular fluids as rapidly and completely as possible consistent with the patient's safety and comfort and, once this is accomplished, the prevention of its re-accumulation. It matters little which diuretic preparation is used, as long as it produces the desired effect and is well tolerated. It is far better to produce a mild or moderate diuresis daily, thereby slowly but progressively draining off the excess extracellular fluid, than to produce a copious diuresis at wider intervals during which the patient may re-accumulate a good part of the fluid thus eliminated. A large diuresis is a dramatic episode but it frequently leads to unpleasant and occasionally dangerous complications, such as severe fatigue, exhaustion and sometimes collapse, acute bladder retention, and undue loss of electrolytes and water-soluble vitamins. Such reactions have often been erroneously considered toxic manifestations of a particular drug, instead of the consequence of excessive therapeutic action and, therefore, a testimonial to its potency.

Since the amount of diuresis is influenced not only by the potency of the drug but also, and often to a much greater extent, by the amount of retained fluid, a smaller rather than a larger dose should be employed in the initial treatment of the "waterlogged" patient. Observation of the response will determine the size and frequency of subsequent doses. In this manner, therapy is individualized so that each patient shows a gradual and progressive decline in weight until all of the edema has been eliminated.

As emphasized by Gold,[1] the daily weight is the most practical guide to the adjustment of the regimen for the individual patient. Except on a rigidly controlled metabolism service, measurements of fluid and electrolyte balance are grossly inaccurate. The clinical signs of failure cannot be quantitated and often indicate migration of the extracellular fluid rather than

its elimination. An accurate record of body weight can easily be obtained even in the home. A weight loss indicates the adequacy of the current regimen in the face of persistent lung rales or pitting edema that might otherwise impel its intensification with resultant toxicity. Conversely, failure to lose weight demonstrates lack of effect and calls for prompt attention. The diuretic dose may be increased or adjuvant measures introduced at once, instead of prolonging the patient's course by continuing the inadequate regimen until the lack of progress becomes manifest.

Once the excess extracellular fluid has been cleared, many patients can be maintained satisfactorily on digitalis and a salt-poor diet without further diuretic therapy. On the other hand, there are also many who are either unable or unwilling to limit their sodium intake sufficiently, or in whom the degree of cardiac impairment or the presence of complicating factors cannot be overcome by these measures alone. Diuretic therapy must then be continued indefinitely and, often, permanently. In these cases the selection of the drug and determination of its dose and frequency of administration are dictated by the requirements of the individual patient.

Each case must, therefore, be observed carefully and the diuretic therapy adjusted to offset changes affecting the patient's ability to maintain optimal cardiac compensation. These may be such profound changes as the difference in control of sodium intake between a hospital diet, a diet served in the home, and a diet involving one or more meals in restaurants; the increase in amount of physical activity as the patient passes from convalescence to partial and, ultimately, complete resumption of his normal work load; or the effect on the heart of progressive disease, pathology in other organ systems or intercurrent infection. They may be relatively minor in degree, i.e., fluctuations in weather and environmental temperature and humidity. Their importance depends not so much on any absolute measurement as on their effect on the patient. Some individuals can tolerate without symptoms relatively large fluctuations in degree of failure as measured by the amount of excess extracellular fluid retained. Others are more delicately balanced, having symptoms of overdehydration at one level of body weight and symptoms of heart failure when only a few pounds heavier.

As in the initial treatment of failure, fluctuations in the patient's body weight represent the most useful and accurate guide to maintenance diuretic therapy. A rise in weight is an indication for increasing the dose of the diuretic drug. At times, however, this fails to yield any additional diuresis or the increased dose produces toxic symptoms. One must then either employ another more potent drug, or return to the original dose and add another drug whose complementary action will produce the desired increase in diuresis.

Increasing the amount of the diuresis may not always be desirable. A weight loss of more than three or four pounds in one day may lead to the symptoms of overdiuresis mentioned above. These may be avoided by using the original dose at more frequent intervals.

A constant weight curve suggests that the diuretic effects of the drug exactly balance the tendency to retain fluid and that the regimen should be continued unchanged. Sometimes it means that the tendency to fluid retention has diminished or disappeared and that the diuretic drug may be unnecessary. This can be determined by either using a smaller dose or using the same dose less frequently. It may be desirable to switch to a drug of lesser potency if it is more convenient or less expensive for the patient. In any case, the intensity of diuretic therapy is gradually diminished, until a rise in weight signals the re-accumulation of edema or it becomes apparent that the patient will maintain optimal compensation without any drugs at all.

EVALUATION OF CHLOROTHIAZIDE AS A DIURETIC AGENT

The usefulness of a diuretic agent in the treatment of heart failure will, therefore, depend upon the following considerations: (1) potency; (2) development of tolerance or the loss of potency when used continuously; (3) incidence of undesirable local and systemic effects after single doses and after continued use; (4) acceptance by patients, i.e., ease of

administration and low cost. These criteria may be applied to the experience with chlorothiazide summarized earlier in this report.

Potency: Chlorothiazide proved to be a diuretic of sufficient potency to make it singularly useful in treating cases of heart failure both in the initial treatment of acute congestive failure and in maintaining optimal compensation in patients requiring continued therapy. It was also effective in cases in which the fluid retention was either caused or enhanced by various alterations in endocrine balance.

Because much of the interest in chlorothiazide stems from reports of its diuretic potency, comparison with other effective diuretics seems inescapable, particularly when examination of some of these reports fails to reveal evidence to substantiate the claims made in them. For example, Bayliss *et al.*[7] claim that chlorothiazide "is often effective when mercurials fail" because 9 of 11 patients who showed "little or no response to biweekly injections of 2 ml. mersalyl" showed a good or fair response to daily doses of chlorothiazide. Similarly, Fishman *et al.*[8] consider oral chlorothiazide "probably superior" to agents comparable in efficacy to "standard parenteral diuretic therapy." Their group of 87 ambulatory patients had also been treated with a biweekly mercurial injection or an oral aminouracil supplemented by periodic doses of the mercurial. They excluded any patient "who was considered as being satisfactorily treated" by this regimen. While chlorothiazide in daily doses up to 3.5 g was effective as a diuretic, they list 11 cases as "therapeutic failures" (6 who demonstrated no diuretic response and 5 who discontinued the drug due to nausea) and 25 patients who continued to require regular mercurial injections: 2 every three weeks, 5 every two weeks, 11 weekly, and 7 biweekly. Thus, chlorothiazide was not able to control the failure in more than one third of the cases.

In both reports chlorothiazide is considered to be equal to or better than the injected mercurial, although the former was given at least once and usually twice each day, while the latter was given only twice a week. A similar argument would lead one to conclude that oral codeine is greater in analgesic potency than is morphine by injection, because the former completely relieves pain when taken several times a day and the latter fails when injected several times a week. It appears likely that more frequent injections of the mercurial probably would have provided much better control of the failure in these cases; and it may be presumed that at least some might have responded equally well to other oral diuretics admittedly less potent than chlorothiazide, if given with comparable frequency.

As with most drugs, the potency of a diuretic can be measured accurately only by using a standard bioassay technic. However, the results of the assay can be transposed directly to clinical practice only if the routes of administration are the same and the effect measured in the assay of the drug is identical or comparable to the effect desired in its clinical application. Reliance on measurement of sodium excretion as the measure of diuretic potency[4] overlooks the possibility that other electrolytes and indeed mechanisms aside from the inhibition of tubular resorption may influence the effectiveness of diuretics. Performance of the assay on patients "who had been in mild heart failure but who at the time of the study were free of edema"[9] is particularly misleading since it is well recognized that the diuretic response shows great variation both in the total amount and the relative proportions of electrolytes and water excreted depending on the amount of fluid and salt retained as well as the presence or absence of congestive failure. It is also imperative to repeat the measurement of effects of comparable doses of the "known" drug used as the reference standard each time a new compound is assayed. Comparisons of the dosage-response ratio of one drug with the data on another drug derived at another time and perhaps in another group of subjects are not valid, particularly when diuresis, a complex phenomenon not yet completely understood and so easily influenced by extraneous factors, is the effect being measured. A reliable method for the bioassay of diuretics in ambulatory patients with congestive heart failure was developed in our clinics some years ago;[10,11] and until it has been applied to the study of chlorothiazide, definitive statements regarding its therapeutic po-

tency in heart failure are not warranted.

The data in this report amply illustrate this point. If 2.0 g of chlorothiazide orally is equal in potency to 2 cc of meralluride intramuscularly as shown in the figures published by Ford[4] and by Moyer,[12] patients well maintained on the latter should be controlled equally well by oral doses of chlorothiazide given with identical frequency. It was usually found, however, that chlorothiazide doses had to be given two or three times as often in order to keep the patient's weight at a constant level. Thus, although these drugs may be equal in saluretic potency in single dose trials in nonedematous patients, chlorothiazide appears to be less potent as a diuretic in patients with heart failure given repeated doses. It does, nevertheless, as stated above, have sufficient potency to serve satisfactorily as the sole diuretic in most of the cases of heart failure, both in the initial treatment and maintenance regimens. There was an occasional case in which no significant effect was noted although the patient did respond to a mercurial; these failures of action cannot be explained by the information available.

Tolerance: In contrast to the carbonic anhydrase inhibitors and the aminouracils, which rapidly lose their effectiveness on repeated administration, chlorothiazide seemed to retain diuretic potency after weeks and even months of continuous use. Although a few patients manifested drug tolerance within the period of observation, suggesting that it occurs more often than with the meralluride, signs of tolerance were not frequent enough to suggest the routine interruption of dose schedules. The prompt response to a mercurial injection by the patients who became resistant to chlorothiazide indicates that these were instances of true drug tolerance rather than overdepletion of sodium or other electrolytes.

Toxicity: In assessing the untoward reactions produced by chlorothiazide it is important to separate the effects of its diuretic action from those which represent true toxicity. The former may be produced by any diuretic of sufficient potency and generally indicate the use of excessive doses or electrolyte depletion following prolonged use. As a rule, these can be avoided by more accurate adjustment of the regimen to the particular requirements of the patient. While several doses may have to be omitted, they do not require the abandonment of the drug. Those seen in this series of cases (Table II) did not appear to differ materially in incidence or severity from those seen following mercurials. Although lowered serum potassium levels were found in a few cases (electrolyte levels were determined at irregular intervals and not in every case) clinical manifestations of hypokalemia were not encountered. Reports of potassium depletion[7,13] had prompted the routine prescription of potassium salts or a daily ration of orange juice for all patients on prolonged chlorothiazide therapy.

TABLE II
Untoward Reactions to Oral Chlorothiazide

	Number of cases
Effects of Diuretic Action	
Electrolyte depletion	1
Elevated blood uric acid level	1
Low blood potassium level	3
Acute urinary retention (prostatism)	1
Toxic Effects	
Gastrointestinal irritation	5
Idiosyncrasy	1 (?)

Except for one questionable case of idiosyncrasy, gastrointestinal irritation was the only toxic effect of chlorothiazide noted in this series. It appeared much less frequently than with any other available effective diuretic for oral use.

It is worth noting that in two cases, the gastric symptoms were corrected by giving the drug after meals instead of in the fasting state. Comparisons of hourly urinary output indicated that although the diuresis was slightly delayed in onset and appeared less pronounced when the drug was given after food, the total amount of urine excreted was not diminished.

Acceptability: Except for the few cases of gastrointestinal irritation and those in which chlorothiazide proved "unsatisfactory," all of the patients were pleased with the opportunity to use this new drug. All were delighted to be relieved of the inconvenience of taking injections.

Two patients, however, expressed a desire to return to the mercurial injections when chlorothiazide was released commercially and they were given prescriptions to be filled at a pharmacy instead of the free bottles of tablets that were provided by the manufacturer for this study. These patients had extremely limited incomes, already strained by costs of their other medications and special diets. The average cost of a day's supply of chlorothiazide is roughly comparable to that of the mercurial and, in addition, permits saving the cost of hypodermic injections. The necessity of taking it daily, however, made it twice as expensive as the three mercurial injections per week each had previously required—both patients had been trained to administer the injections to themselves—and there was the added cost of the potassium supplements deemed advisable for patients on continuous chlorothiazide therapy. This additional burden was too much for their slender resources.*

Summary and Conclusions

(1) Chlorothiazide was administered orally in 61 cases of congestive heart failure, 13 cases of heart disease with failure precipitated by endocrine imbalance, and 24 noncardiac cases with fluid retention of endocrine etiology.

(2) Chlorothiazide alone satisfied the diuretic requirements of 85 (87 per cent) of the entire series of 98 cases.

(3) Most patients required doses ranging from 1.0 g to 2.0 g/day; doses higher than 2.0 g/day appeared to have no additional effect.

(4) Patients previously maintained on parenteral mercurials required more frequent doses of chlorothiazide to achieve comparable results.

(5) Instances of lack of effectiveness and development of tolerance appeared to be somewhat more frequent than with parenteral mercurials, but much less frequent than with any other currently available oral diuretic.

(6) Chlorothiazide exhibited no significant local or systemic toxicity other than a few instances of gastrointestinal irritation.

(7) Low blood potassium levels were noted in a few cases but none of the clinical disturbances associated with potassium depletion were seen.

(8) Chlorothiazide is a satisfactory oral diuretic both for the initial treatment and the maintenance of most patients with congestive heart failure.

(9) Its ease of administration does not eliminate the necessity of continued careful observation and the individualized adjustment of dosage schedules to meet each patient's changing requirements.

* These cases illustrate the all too frequent predicament of the unfortunate patient with a fixed marginal income confronted by today's higher cost of living, and should not be regarded as criticism of the pricing policies of the drug manufacturer.

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Angina Pectoris

Its Alleviation with Chlorothiazide

FRANK A. MARSHALL, M.D., F.A.C.C.

Weehawken, New Jersey

ANGINA PECTORIS is a subjective disease, a syndrome characterized by pain. Its diagnosis and evaluation are based solely upon a patient's perception of this discomfort. Few complain unless pain is definite and moderately severe. Correlation with effort is promptly noted. In spite of all the electrical and chemical advances in the study of the disease, angina pectoris remains diagnosed much as it did in Heberden's time—upon a careful history of the type, location and distribution of pain.[1] Relief with sublingual nitroglycerin and with cessation of the inciting effort is confirmatory and helpful in substantiating the diagnosis. The electrocardiographic findings are usually equivocal, but may reveal associated cardiac disease as well as abnormal changes with the exercise or anoxemia tests. It should be stressed that coronary insufficiency is not necessarily the syndrome of angina. Myocardial anoxemia can result from causes other than coronary insufficiency.

EFFECT OF CHLOROTHIAZIDE ON ANGINA

The discovery of the beneficial effects of chlorothiazide on anginal pain was accidental. It was not anticipated. It was during an investigation of its diuretic properties that the benefits of chlorothiazide (Diuril) in angina were incidentally, but prominently, revealed. Patients reported improvement in their pain and their work tolerance. Each patient had previously been on regimens to procure relief of longer duration than that of nitroglycerin. Pentaerythritol tetranitrate, triethanolamine trinitrate biphosphate, nitroglyn, and papaverin were among the many drugs tried, in addition to the theophyllines, sedatives, and vasodilators, including nicotinic acid amides and iodides. They were uniformly disappointing. In not one instance was information of substantial relief volunteered or elicited upon questioning. In a good many of these cases, the patient was prepared to expect improvement. Nothing comparable to the patient acceptance and enthusiasm for chlorothiazide was ever evoked by the above groups of drugs. The broadened concept of the etiology of angina pectoris can explain the lack of uniform response to the above group of drugs.

The improvement obtained with chlorothiazide was, at least, in part, associated with its saluretic properties. Although Beyer *et al.*[2] state, "The compound does not possess anticonvulsant, cardiovascular, local anesthetic or analgesic activity," the result was very clear-cut and of such appreciable extent to be readily noted by patients, strongly suggesting causal sequence. The prompt response (two hours) and a continued response for 6 to 8, possibly 12 hours, facilitated judging the effects of chlorothiazide on anginal symptoms. Most patients, but not all, noticed that increased urinary flow was initially prominent, but later became less perceptible. One patient noticed no appreciable (to him) diuresis. The mechanism of relief was probably achieved through a reduction of blood volume, removing an added burden of an already overburdened heart. As the diuretic effect waned, so did generally the relief from angina. Nevertheless, substantial benefits were effected, even when no apparent diuresis resulted. Two of the patients reported did not note any diuresis. As an added experimental effort, the drug was dis-

TABLE I

25 Cases of Angina Pectoris Treated with Chlorothiazide

Number	Case	Sex	Age	Duration of symptoms prior to therapy (months)	Results		Diuresis	Remarks
					Excellent	Fair		
1	R. C.	F	66	12	x		++	See case discussion
2	J. E.	M	61	Years		x	−	See case discussion
3	H. L.	F	69	24	x		+++	See case discussion
4	W. M.	M	70	24		x	++	See case discussion
5	B. I.	M	60	18	x		−	See case discussion
6	P. V.	M	64	28	x		+	Anterior myocardial infarction 7 years previously
7	A. S.	M	56	11	x		+++	Slightly obese
8	M. W.	F	73	16		x	−	
9	G. B.	M	65	4	x		+	Bronchopneumonia 5 months previous
10	A. W. (Mrs.)	F	62	3		x	+	Had to retire because of chest pain
11	S. W.	M	64	1	x		+	
12	A. W.	F	76	7	x		++	Anterior myocardial infarction 2 years previous
13	R. V.	M	85	12		x	++	
14	M. O.	F	60	8		x	+	Emotional tension at home
15	R. P.	F	60	6		x	+	
16	F. F.	F	56	12		x	−	Valvular heart disease: Mitral insufficiency and left ventricular hypertrophy. B.P. 196/96
17	M. S.	F	58	3		x	+	Very obese
18	A. M.	M	61	6		x	+	Spastic colitis present
19	M. M.	F	70	12	x		++	Slight edema of legs
20	E. K.	F	72	26	x		+	Blood pressure declined during therapy
21	L. K.	F	48	2		x	+	Diabetic
22	C. E.	F	55	6 Very severe for 3 weeks preceding trial	x		+	Very obese and severe diastolic hypertension
23	J. C.	M	68	24		x	+	Also relieved fairly well by Metamine
24	R. F.	F	55	2		x	++	Slightly nauseated on 1.5 g, but not on 1.0 g daily
25	L. J.	F	51	30		x	+	Aortic stenosis, severe anxiety

continued. Each patient requested its return.

Another observation indicated strongly that it is very difficult to evaluate any long-acting drug for the relief of angina. First, one must be guided by subjective, symptomatic responses. This limitation of observation to gross effects primarily dispenses with the niceties of accurate, quantitative measurements. Secondly, the syndrome of angina is a warning system, designed to protect the heart by warding off excess stresses and strains. To curtail so vital a function would be hazardous and rob the patient of improved chances for survival. Hence, any longer-acting drug must be only partially effective from an ideal standpoint. Some evidence of cardiac stress must remain. However, relief from the agonizing pain must occur. Sublingual nitroglycerin is thus ideal for immediate benefit, with chlorothiazide producing subsidence of pain as measured in hours instead of minutes. Usually when relief occurs and is somewhat more lasting, the patient performs more activity than desired. So pain reaction at this point is welcome from a cardiac standpoint. Caution should still be stressed. The patient must be advised that no pill can "cure" heart disease, particularly angina pectoris.

Case Data

Twenty-five cases, fifteen females and ten males, generally in the 6th and 7th decades of life, constituted the trial program (Table I). Eleven patients had excellent results and fourteen had fairly good results. Everyone felt some degree of improvement. During the trial period no one felt any worse. Four cases had no evi-

dent diuresis, at least as far as the patient was able to observe. The rest noticed definite diuresis which usually became less pronounced with the continuation of therapy, i.e. as the patient became "drier."

Doses were standardized at one tablet twice daily, 0.5 g per tablet. The only adverse effect was slight nausea in one patient who increased dosage to 1.5 g daily.

Dosage was continued for about ten days, after which it was continued as patient required relief, but always 1 g daily was given and maintained until diuresis either clinically ceased or pain was substantially relieved. Most patients asked for more tablets when their supply was depleted.

All of these patients were office cases while the trials were in progress. This gave an opportunity for observation during the experiment while these patients were in their normal environments.

Illustrative Cases

Case 1. R. C., female, age 66, complained of shortness of breath and severe pains in the left chest, chiefly substernal, spreading down the left arm. This was strongly aggravated by excitement. Blood pressure varied from 176/98 to 220/106. This syndrome had been present for over a year. Left ventricular hypertrophy was present and also noted on the electrocardiogram. Sedatives, vasodilators, and the usual panel of drugs for angina failed to produce effective relief of pain. Rest and nitroglycerin were helpful. The latter was used infrequently because of annoying side effects.

On February 5, with blood pressure 220/106, severe episodes of substernal pain occurred, spreading to left shoulder, medial surface of left arm and forearm, and down to the left 4th and 5th fingers. The making of beds in the morning caused very severe pain, requiring an hour's rest for recovery.

On chlorothiazide, 500 mg twice daily, pain improved, "not so much down the arm." Only a small residual remained of the substernal pain, and the blood pressure was 156/94. All edema of the legs disappeared. By February 20, the patient volunteered information, "pills stopped pain in my left arm and I don't have pain in my front chest." She also noted some diuresis. Chlorothiazide has been the most effective of any medicament taken over the past two years.

Case 2. J. E., male, age 61, with arteriosclerotic heart disease, left bundle branch block, and peripheral vascular disease of both legs, had angina for many years. His blood pressure was 106/74. On digitalis, sedatives, the usual gamut of anginal pain relievers, iodides, niacin, the patient experienced indifferent results. Rest and nitroglycerin again were the mainstays of relief and treatment.

After a week's trial on chlorothiazide, he noted definite improvement. "I didn't have to take as many nitroglycerins." No diuresis was apparent, although, upon questioning, urine was reported as "enough."

Case 3. H. L., female, age 69, had arteriosclerotic heart disease and slight edema of the legs. Her blood pressure was 152/76. She complained bitterly of severe substernal and also subscapular pains. The latter had a tendency to radiate anteriorly. On October 14, 1957, chlorothiazide was tried on a twice daily basis, chiefly with the thought of removing the edema. She was ecstatic in praise of relief of pain. Increased amount of urine was passed shortly after ingestion. By November 8, blood pressure was 132/72; chest pain was much milder and did not recur so often. The edema of the legs was gone. The drug was discontinued in December, only to have anginal pain recur as well as the edema of the legs. Chlorothiazide again provided relief for both complaints.

Case 4. W. M., male, age 70, had been suffering from substernal distress for two years, causing his retirement as an active plumber. His blood pressure was 170/88. On digitalis and the usual gamut of drugs for anginal pain, only rest and nitroglycerin eased this patient effectively. Chlorothiazide caused definite improvement. "I need fewer pills under my tongue and I can walk much further than previously before I need a nitroglycerin." Diuresis was noted by this patient.

Case 5. B. I., male, age 60, with arteriosclerotic heart disease, complained of severe pain in the chest which prevented him from following his occupation as a barber. The blood pressure was 116/78. Previously digitalized, he experienced noticeable relief on two 500 mg tablets of chlorothiazide daily. He volunteered data that only slight pain now occurred on effort. Recurrences of pain were less frequent. No marked diuresis was noted.

Conclusions

Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide), well known as an orally effective, new nonmercurial saluretic and diuretic, was instrumental in providing significant relief of the anginal syndrome. This information, not originally sought, was volunteered by its victims. As "the criterion of benefit is relief of anginal pain,"[3,4] chlorothiazide admirably fulfills this requirement. It has been, in my experience, the most effective nitroglycerin sparer of all drugs recommended so far. Chlorothiazide provides subjective relief—

relief distinctly noticed and gratefully appreciated by thankful patients.

2202 Palisade Avenue
Weehawken, New Jersey

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The Management of Congestive Heart Failure with a Free Salt Intake*

IRWIN S. ESKWITH, M.D., F.A.C.C.

Bridgeport, Connecticut

THE accumulation of fluid or edema is the most obvious external manifestation of congestive heart failure. It is not surprising, therefore, that one of the early forms of therapy for this condition was the restriction of fluid. However, this was not found to be as effective as hoped for and the search for more effective measures was continued. The introduction of organomercurials as diuretics represented a great advance in the management of congestive failure. Although these compounds were highly effective, many clinicians found it difficult to dissociate the benign diureses of meralluride and similar substances from the more nephrotoxic effects of the inorganic mercurial salts. It was then found that cardiac patients also handled salt poorly, particularly so far as the sodium ion was concerned, and that a cardiac patient would excrete less in a given period of time than a noncardiac. This resulted in the Schemm regimen[1] based on the assumption that if a cardiac patient is given liberal amounts of water without salt, the excess sodium will be flushed from the body. This regimen might also have represented a healthy reaction to the older method of fluid restriction. Although some early success was reported,[2] the high-fluid, salt-free regimen proved ineffective. However, the importance of sodium restriction as the foundation for the therapy of congestive failure has gained general, or almost general, acceptance.

Not only was sodium, primarily salt, intake restricted, but various preparations were introduced to rid the body of sodium. This therapy was pursued, although the interstitial fluid is primarily a dilute saline solution containing as principal cation and anion sodium and chloride, and that within this solution other ions are dissolved. This has been wistfully referred to as the chain binding us to the salty sea from which we crawled eons before the man-made satellites were launched into their orbits. Ample evidence of the great need for salt is shown by the great animal treks for this substance and by the value placed in primitive societies upon this mineral. Thus it could be surmised that some dangers would be associated with the overzealous restriction of such an important substance.

Medical history reveals that when a really effective drug or method of therapy becomes available, it rapidly replaces older and less effective methods of therapy. Thus, sulfonamides and penicillin replaced biologic preparations rather quickly in the therapy of certain infectious diseases. The closing of the Trudeau Sanatorium and similar institutions offering bed rest as the keystone of antituberculous therapy is dramatic testimony to the efficiency of streptomycin and other drugs in the therapy of tuberculosis.

At times fundamental physiologic data have no obvious connection with the therapy of a disease. Illustrative of this is the therapy of gout. Benemid, a potent uricosuric agent, neither aborts nor prevents attacks of gouty arthritis better than the older drug colchicine. Yet the use of colchicine is entirely empiric. Its pharmacologic activity remains a mystery.

Had sodium retention *per se* been the cause of cardiac edema, then its restriction, while the

* From the Department of Medicine, St. Vincent's Hospital, Bridgeport, Connecticut.

kidney was slowly excreting the body excess, should have eliminated the fluid accumulation. However, clinically, except in very mild cases of congestive failure, this is not so, and mercurial diuretics remained popular. In fact, in the past ten years, up to the introduction of chlorothiazide, the sales of at least one mercurial diuretic continued to rise.[3]

Because of the obvious inadequacy of dietary sodium restriction, various substances have been introduced which were aimed at removing sodium, in excess of chloride, from the body. The first of these were the cation exchange resins.[4] Not only were these nugatory, but they caused both local (gastrointestinal) distress and at times systemic disturbances.[5,6] A second preparation, acetazolamide (Diamox), a carbonic anhydrase inhibitor, was aimed at removing sodium via the renal route rather than the gastrointestinal tract. The author has found acetazolamide to be an ineffective drug in the management of heart failure, a view supported by Relman, Leaf, and Schwartz,[7] although Friedberg[8] has found it more satisfactory.

The restriction of sodium in treatment of heart failure was frequently ineffective, and shortly after its use became widespread, reports of unfavorable reactions began to appear in the literature. Schroeder[9] in 1949 reported a group of patients dying edematous, uremic, and hyponatremic and dubbed the condition "the low salt syndrome." Although he believed that death was due to renal failure, the mechanism of this failure is unexplained. He recommended the use of hypertonic saline as therapy. However, this procedure has met with indifferent success in our hands[10] as well as in those of others.[11] Black and Litchfield[12] stated that no uremic deaths had occurred in their cardiacs treated with mercurial diuretics until sodium restriction was added to the regimen. They advocated a free sodium intake for patients who required mercurial diuretics. Although they found no pathologic alterations in the kidneys to account for the renal failure, tests of renal function showed marked depression after the sodium-free regimen had been instituted. Citron and his associates[13] reported similar complications, but attributed them to the use of mercurial diuretics rather than the lack of salt.

The purpose of this paper is to illustrate that cardiac patients can be maintained edema-free without restricting their salt intake. Such a paper had been planned for some time, using as subjects patients who had been maintained on regular injections of meralluride. However, the introduction of chlorothiazide (Diuril) has made maintenance even more satisfactory. As a result, the present series is presented to demonstrate the effectiveness and safety of this program.

Material and Methods

Twenty-three patients have been studied. With one exception (case 22), these have been private patients with heart disease of diverse etiologies. Table I summarizes the essential data. The age of the patients varies widely, with an average of 61 years. Fourteen are males and nine are females. The longest period of treatment (case 8) has been 84 months, the shortest, three months, with an average of 20 months. The table summarizes treatment before and after the introduction of chlorothiazide. Patients' weights have not been given in the table because as time has passed, some of the older people have actually lost more weight than in my opinion can be accounted for by fluid loss and some of the more seriously ill patients have gained weight without visible accumulation of edema, which probably represents the result of better health. The type of failure, i.e., right or left, is indicated under the etiology.

With the mercurial diuretics it had been our practice to administer them often enough to prevent either fluid reaccumulation or the appearance of dyspnea. Chlorothiazide is now used as the mainstay of diuretic therapy and mercurial diuretics are given often enough to supplement this action, when necessary. Experience to date suggests that in the future the use of mercurial diuretics will further diminish.

At present the procedure used in treatment of congestive failure is digitalization, a priming injection of a mercurial diuretic, and then chlorothiazide 0.5 g t.i.d. for one week and 0.5 g b.i.d. for maintenance. Free salt intake is

TABLE I

Summary of Treatment in 23 Cases of Congestive Heart Failure

Case	Present age	Sex	Etiology and type of failure	Duration of therapy (months)	Previous diuretic therapy	Present diuretic therapy since December 1957	Urea nitrogen initial (mg%)	Urea nitrogen present (mg%)	Result
1. P. A.	68	Male	Arteriosclerotic heart disease, right heart failure	8	Meralluride	Chlorothiazide 0.5 b.i.d.	15	15	Excellent
2. I. F.	58	Male	Arteriosclerotic heart disease and old infarction, combined heart failure	10	None	Chlorothiazide 0.5 b.i.d. Meralluride 2 cc weekly	19.5	18.0	Poor
3. J. S.	73	Male	Arteriosclerotic heart disease, right heart failure	5	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.25 b.i.d.	—	—	Excellent
4. E. C.	70	Female	Arteriosclerotic heart disease, combined heart failure	10	Meralluride 2 cc twice weekly	Chlorothiazide 0.5 b.i.d. Meralluride 2 cc weekly	15	10	Excellent
5. J. C.	29	Male	Congenital; tetralogy of Fallot, right heart failure	12	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.5 b.i.d. Meralluride occasionally	28	22	Fair
6. L. O.	70	Male	Arteriosclerotic heart disease, right heart failure	12	Meralluride 2 cc weekly	Meralluride 2 cc weekly	—	—	Excellent
7. S. S.	45	Female	Rheumatic heart disease with mitral stenosis and mitral insufficiency, left heart failure	35	Meralluride 2 cc weekly	Chlorothiazide 0.5 b.i.d. Meralluride occasionally	—	—	Excellent
8. S. G.	70	Male	Hypertensive cardiovascular disease, left heart failure	84	Meralluride 2 cc weekly	Chlorothiazide 0.5 b.i.d. Meralluride 2 cc q. 2 weeks	19	11.7	Fair
9. A. R.	81	Male	Hypertensive cardiovascular disease, combined heart failure	10	Meralluride 2 cc weekly	Chlorothiazide 0.5 b.i.d.	22	18	Excellent
10. P. A.	62	Female	Arteriosclerotic heart disease, right heart failure	62	Meralluride 2 cc weekly	Same as previously	26.0	16.5	Excellent
11. P. C.	68	Male	Hypertensive cardiovascular disease, combined heart failure	13	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.5 b.i.d.	30	26	Excellent
12. M. M.	75	Male	Arteriosclerotic heart disease, combined heart failure	14	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.5 b.i.d.	—	—	Excellent
13. E. B.	39	Female	Rheumatic heart disease with mitral stenosis	11	Meralluride 2 cc q. 3 weeks	Chlorothiazide 0.5 b.i.d. Meralluride occasionally	—	—	Fair
14. E. G.	76	Male	Cor pulmonale, right heart failure	23	Meralluride 2 cc q. 3 weeks	Chlorothiazide 0.5 b.i.d.	—	—	Excellent
15. M. R.	48	Female	Hypertensive cardiovascular disease and arteriosclerotic heart disease	28	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.5 b.i.d. Meralluride 2 cc q. 3 weeks	24	17.0	Fair
16. R. H.	76	Female	Arteriosclerotic heart disease, left heart failure	50	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.5 b.i.d.	17	17	Excellent
17. M. L.	36	Female	Rheumatic heart disease, mitral stenosis, valvotomy, right heart failure	28	Meralluride 2 cc q. 3 weeks	Chlorothiazide 0.5 b.i.d. Meralluride occasionally	18	18.5	Excellent
18. V. S.	53	Female	Rheumatic heart disease, mitral stenosis, left heart failure	4	—	Chlorothiazide 0.5 b.i.d.	14	14	Excellent
19. B. O.	65	Male	Cor pulmonale, arteriosclerotic heart disease, right heart failure	7	Meralluride 2 cc q. 2 weeks	Chlorothiazide 0.5 b.i.d.	—	—	Excellent
20. G. H.	77	Male	Arteriosclerotic heart disease, right heart failure	5	—	Chlorothiazide 0.5 b.i.d.	21	22	Excellent
21. J. R.	72	Male	Arteriosclerotic heart disease	3	—	Chlorothiazide 0.5 b.i.d.	—	—	Excellent
22. A. M.	26	Female	Rheumatic heart disease, mitral stenosis, myocardial insufficiency	34	Meralluride 2 cc weekly	Chlorothiazide 0.5 b.i.d.	26	20	Excellent
23. J. F.	83	Male	Arteriosclerotic heart disease	4	—	Chlorothiazide 0.5 b.i.d.	22	18	Excellent

permitted. There are two exceptions to this general treatment scheme. A 62-year-old woman (case 10) has continued on meralluride weekly because of intolerance to chlorothiazide. She is free of edema and able to pursue all activities. Another man (case 3) had moderate intolerance to chlorothiazide and takes only 0.25 g b.i.d.

Results of Treatment

The results have been excellent in 19, fair in 3, and poor in 1 patient. "Excellent" does not imply any change in the fundamental cardiac state. It refers to the complete absence of dyspnea and/or edema, and relatively full activity. "Fair" indicates incomplete relief of edema or dyspnea, or the passage of at least two years without an episode of decompensation; and "poor" implies little relief of these symptoms or a break in compensation after a short period of therapy.

The renal status of the patients is indicated by BUN determinations at the start of any type of diuretic therapy and at present (Table I). As can be seen, there is no evidence of renal insufficiency or progression of existing insufficiency in the patients who have had BUN determinations performed.

Due to the short period of observation with chlorothiazide, no definite statements can be made as to eventual renal toxicity, but there has been no evidence of renal damage in this group thus far, and some of these patients have received liberal amounts of meralluride prior to chlorothiazide therapy.

Illustrative Case Histories

Case 1. Patient is a 68-year-old male who was admitted to St. Vincent's Hospital on August 8, 1957. For two weeks he had noted severe swelling of both legs, dyspnea and nocturnal orthopnea. Physical examination revealed an elderly male with distended neck veins, moderate dyspnea at rest and marked edema of both legs. The heart was enlarged to the left with the apex in the 6th interspace at the anterior axillary line. The heart rate was 100 and the rhythm was grossly irregular. The liver was palpable 3 cm below the costal margin and was tender. There was dullness at the right base, and medium moist inspiratory rales over the lower portions of both lung fields. ECG showed auricular fibrillation and nonspecific changes suggesting chronic myocardial insufficiency.

The patient's admission weight was 136 lb. He was digitalized with 1.2 g of whole leaf digitalis and given Mercuhydrin, 2 cc i.m. every other day for a period of eight days, at the end of which time his weight had fallen to 130 lb. He was then discharged to my office. He continued to receive Mercuhydrin once weekly. His weight fluctuated between 128 and 130 until November 15, 1957, when edema began to reaccumulate.

He was readmitted to St. Vincent's Hospital on December 2, 1957, with findings similar to the first admission and weight equal to 135 lb. After two injections of Mercuhydrin over a six-day period, his weight fell to 126 lb. He returned to office management. At this time chlorothiazide became available and the patient was started on 0.5 g t.i.d. for one week and then 0.5 g b.i.d. He was instructed to eat what he wished and as salty food as he desired. His weight has remained constant at 126 lb. He has required no Mercuhydrin since and is well maintained on chlorothiazide.

Case 2. This man was first seen at the age of 55, in June, 1955. His chief complaint was intermittent substernal pain radiating to the back. These episodes were of short duration and were worse upon exertion or excitement.

Physical examination revealed an extremely apprehensive male. The blood pressure was 150/100. The lungs were clear. Heart rhythm was normal and fluoroscopy revealed a normal-sized heart. Electrocardiogram showed a Q_3T_3 pattern with upright T waves in all other leads. He was given sedation and permitted to continue his occupation.

In July, 1957, he was admitted to St. Vincent's Hospital under another physician's care because of more severe substernal pain. Electrocardiograms taken showed inversions of the T wave in leads 2 and a VF in addition to the earlier changes, and he was hospitalized for 2 weeks with a diagnosis of myocardial infarction.

In January, 1958, he developed nocturnal dyspnea and orthopnea. Physical examination revealed moist rales in both lung fields. The liver was palpable and tender two fingerbreadths below the costal margin. There was no pedal edema. Decholin circulation time was 30 seconds. He was digitalized with whole leaf digitalis and started on Mercuhydrin 2 cc i.m. q. two weeks. On February 8, 1958, dyspnea recurred and he was hospitalized for one week. Chlorothiazide therapy, 0.5 g b.i.d., was instituted and Mercuhydrin every two to three weeks administered.

On March 10, 1958, patient was readmitted to St. Vincent's Hospital with severe pulmonary edema. Blood pressure was 150/90. Electrocardiograms were unchanged except for a 2 mm S-T elevation which returned to normal in five days. He now receives chlorothiazide 0.5 g b.i.d. and Mercuhydrin 2 cc i.m. weekly. For the past month he has been compensated.

Comment: This patient is classified as a poor result because of two episodes of decompensation when he was supposedly on an adequate diuretic regimen. It is possible that more energetic therapy will produce a more satisfactory result.

Case 8. This 70-year-old male was first seen in my office, June 5, 1950. At that time he complained of epigastric and right upper quadrant pain. He had also noticed marked dyspnea on exertion over a three-

month period. He had never noticed nocturnal dyspnea, orthopnea, or ankle edema.

Physical examination at that time revealed a blood pressure of 170/110. The heart was enlarged with the apex 2 cm outside the midclavicular line. The heart rate was 110 and the rhythm was regular. There was a moderately loud, harsh systolic apical murmur. Medium moist rales were audible over the lower one-third of both lung fields. The liver was palpable 5 cm below the costal margin and was tender. Fluoroscopy revealed marked left ventricular enlargement and moderate pulmonary congestion. The electrocardiogram showed left ventricular hypertrophy.

The patient was digitalized with whole leaf digitalis. He was given Mercuhydrin 2 cc i.m. once weekly with complete relief of dyspnea and right upper quadrant pain. Rales disappeared and the liver receded to normal size. On this regimen he continued to work rather strenuously as a baker until September 7, 1957. On this date, while at work, he developed severe dyspnea and was admitted to St. Vincent's Hospital. He was in frank pulmonary edema upon admission and 500 cc of blood were removed by phlebotomy. Morphine and aminophylline were also administered. The pulmonary edema cleared and digitalis was continued. Electrocardiograms showed no evidence of acute infarction. He was discharged on September 17 much improved.

On November 30, 1957, he was readmitted because of cough, fever, and chills. There was dullness and increased breath sounds over the right lower lobe. Chest films revealed consolidation of this lobe. The patient responded well to penicillin and was discharged, once more on his regimen of weekly mercurial injections.

On January 8, 1958, he had a third admission to the hospital because of dyspnea and orthopnea and was again found to be in left ventricular failure. Blood pressure during this admission varied between 170–224 systolic and 90–116 diastolic. Chlorothiazide therapy was added to his regimen in the dosage of 0.5 g b.i.d. He was discharged from the hospital on January 30th. Since then he has been asymptomatic. He receives chlorothiazide twice daily and Mercuhydrin twice monthly. I feel that the mercurial injection may soon be abolished. The patient has not returned to work and because of both age and the cardiac status he is probably permanently disabled.

Comment: This arteriosclerotic and hypertensive cardiac patient was treated for six years with weekly injections of mercurial diuretics. As the chart shows, there was no evidence of renal impairment during this period. He did well until the end of 1957. Rather than restrict salt, we added chlorothiazide to the regimen and the results to date have been very good.

Case 9. This 80-year-old male was first seen in my office on April 16, 1957. He complained of dizziness and headache of two weeks' duration. Blood pressure was 240/140. The fundi showed marked arteriolar narrowing and A-V nicking. The heart was enlarged to the left. The ventricular rhythm was irregular with a rate of 65. The lungs were clear. The liver was palpable 3 cm below the costal margin and was not tender. There was 1+ edema of both ankles, bilateral varicosities and varicose pigmentation of the right leg. Neurological examination was normal. Fluoroscopy revealed a greatly enlarged heart, marked tortuosity of the ascending aorta and a small aneurysm of the descending aorta. The electrocardiogram showed auricular fibrillation and left ventricular hypertrophy. Rauwolfia therapy was instituted and the patient had improved moderately by April 27, 1957.

On May 6, he developed severe, crushing, substernal pain, marked dyspnea, and orthopnea, and was admitted to St. Vincent's Hospital. Admission blood pressure was 170/110. There were signs compatible with pulmonary edema. He was treated vigorously for this and digitalized. Electrocardiograms on admission showed marked inversion of the T waves in leads V_2 to V_5 and 1 mm depression of the S-T segments in these leads. The next day the electrocardiogram showed left bundle branch block in addition to the above findings. Erythrocyte sedimentation rate was 42 mm at one hour, leukocyte count was 14,300 with 72 per cent polymorphonuclear cells. The serum transaminase level was 68 units. It was concluded that the patient had suffered an anteroseptal myocardial infarction. He was treated with anticoagulants and discharged May 23, 1957.

One week after discharge he developed dyspnea, orthopnea, epigastric pain, and increased ankle edema. Examination of the lungs showed rales over the lower third of both lung fields. He was started on intramuscular injections of Mercuhydrin, 2 cc once weekly, maintenance digitalis, 0.1 g whole leaf every other day, and a free salt intake. On this regimen he did fairly well, except for occasional episodes of dyspnea and epigastric distress about the sixth day after each injection. In December, 1957, the patient was given chlorothiazide, 0.5 g b.i.d. Residual dyspnea and epigastric distress disappeared. Ankle edema resolved completely. This was somewhat surprising since it had been felt that some of the edema was due to the varicose veins. Blood pressure is now 170/80 which may represent an added effect of chlorothiazide. He is now seen once monthly and receives no mercurial injections.

Comment: This is an excellent result in a man with extensive arteriosclerosis and cardiac involvement. Three months ago the patient left his daughter's home to return to his own residence and now lives without assistance from his family. He is able to indulge in moderate activity without any symptoms.

CASE 10. This 62-year-old female was first seen in March, 1952, complaining of dyspnea and orthopnea. Examination revealed moderate cardiac enlargement, rapid auricular fibrillation, and a moderately intense mitral systolic murmur. There were moist rales at both lung bases. The liver was palpable to the umbilicus and quite tender. There was moderate edema of the legs and ankles. Weight was 141 lb. She was digitalized and placed on a regimen of 2 cc of meralluride (Mercuhydrin) weekly, intramuscularly. She improved temporarily, but in April, 1952, she developed severe substernal pain, perspiration, and her blood pressure fell from 150/90 to 98/72. Electrocardiograms now revealed normal sinus rhythm and evidence of an acute posterior wall infarction. She was admitted to St. Vincent's Hospital and treated with anticoagulants. Her recovery was uneventful.

After discharge, weekly injections of mercurial diuretics and a free salt intake were continued. In May, 1955, fever, malaise and weakness appeared. There was a marked increase in hepatomegaly and edema of the legs. Physical examination also revealed a petechial hemorrhage in the right conjunctiva. She was admitted to St. Vincent's Hospital where temperatures varied between 99° and 101° F. Three days after admission two new petechiae appeared on the right leg. Blood cultures were consistently negative. However, after consultation with Dr. Paul Beeson, it was decided to treat her for subacute bacterial endocarditis. She received 6,000,000 units penicillin and 1.0 g streptomycin daily for two weeks. Within seven days her temperature returned to normal. She was discharged on her previous regimen. In December she was given chlorothiazide 0.5 g b.i.d. but was unable to take the drug because of gastrointestinal irritation. Accordingly, she has been continued on weekly injections of Mercuhydrin.

Comment: This patient has had an uneventful course since 1955. She is fully active and is presently contemplating a voyage abroad. No signs of renal insufficiency have appeared although mercurial diuretics have been liberally used over a seven-year period. Because of her intolerance to chlorothiazide, the present regimen will be continued.

CASE 22. This 22-year-old Puerto Rican woman with rheumatic heart disease had her first episode of congestive failure in her homeland at the age of 18. After taking up residence in New York City she had several hospital admissions there because of both congestive failure and repeated respiratory infections. During this time, she had been maintained on digitalis, various diuretics, and a salt-free diet. She moved to Bridgeport in 1956 and was followed both in the Cardiac Clinic and the Medical Service at St. Vincent's Hospital.

On June 21, 1957, she was admitted because of severe dyspnea and orthopnea. Examination revealed moist rales throughout both lung fields, irregular heart rhythm, and a loud, double mitral murmur. Electrocardiograms revealed auricular fibrillation and left ventricular hypertrophy. E.S.R. was 48 mm fall/hour. The ASL-O titer was 12 Todd units. Chest films demonstrated marked, generalized cardiac enlargement and severe engorgement of the pulmonary blood vessels. She recompensated with digitalis, mercurial diuretics, and a salt-free diet. On the 17th hospital day, cough, hemoptysis, and right-sided chest pain appeared. Decreased breath sounds were found in the right base. X-ray examination revealed a diminished radiolucency in the periphery of the right lower lobe. In view of her normal temperature, it was felt that this represented pulmonary infarction. She gradually improved and was discharged to the Cardiac Clinic.

On July 18, 1957, she was readmitted to the hospital because of recurrence of right-sided chest pain and dyspnea. On this admission a definite friction rub was heard over the right base. Once more she improved and was treated at the Clinic until October 17, 1957. She was then readmitted with a temperature of 105.6° F, pulmonary edema, and auricular fibrillation. Again there was opacification of the right lower lung field. She was treated with anticoagulants, antibiotics, mercurials, and digitalis. She was discharged, improved, on October 31, 1957.

After this discharge she complained of weakness and dyspnea. The patient was tense and apprehensive. She was instructed to gradually increase her housework and was also told to eat salt freely. She was continued on Mercuhydrin 2 cc i.m. weekly and occasionally twice weekly until January, when chlorothiazide 0.5 g b.i.d. was added to her regimen. For the past three months she has been asymptomatic. She receives meralluride only sporadically, on an average of 2 cc every three weeks. She is able to do some housework and occasionally go out marketing. Her progress has been excellent.

Comment: Mitral valvulotomy has not been performed in this case because the murmur, ECG findings, and chest films all indicate considerable mitral insufficiency. The repetitive character of her admissions in 1957 seriously raises the possibility of rheumatic reactivation. If so, much of her subsequent improvement could be attributed to subsidence of this infection. However, this patient with a seriously damaged heart has done well, remained compensated, increased her activity and morale with digitalis, diuretics, and a free salt intake.

CASE 4. This patient had a long history of arteriosclerotic heart disease and had been treated with diuretics and salt restriction. In spite of this she had had many episodes of pulmonary edema. On free

sodium intake she has done well. In October, 1957, she was hospitalized for staphylococcal pneumonia of the right middle lobe and made an excellent recovery.

CASE 5. This patient had a Blalock-Taussig operation in 1949 with marked improvement in his cardiac status until 1 year ago. He has recently undergone a second similar procedure and since March 1, 1958, has required only digitalis and chlorothiazide.

CASE 7. This is the case of a 45-year-old school teacher who also has considerable household duties. She is not operable because of marked mitral insufficiency. However, her clinical status is excellent.

CASE 11. This is a patient with severe hypertension who in December, 1957, was hospitalized because of mental confusion which may have been due to cerebral thrombosis. His blood pressure remains fairly high at 230/130 but this is less than pre-failure levels of 280/160 even with a free salt intake.

DISCUSSION

Sodium restriction for the control of congestive failure is not an adequate therapeutic measure in most instances. Therefore, it must be combined with diuretics. This combination of a potent diuretic and rigid control of dietary sodium may result in serious abnormalities of renal function and in exacerbation of the decompensated state. Since diuretic measures by themselves are adequate, it appears unnecessary to introduce the added risk of salt depletion. The 23 patients presented in this paper have with one exception remained well or fairly well compensated on a regimen of digitalis and diuretics and a free sodium intake. This has eliminated the tedious task of constant attention to food consumption that many patients find burdensome and others reluctant to pursue. In some instances it has been our impression that the addition of salt to the diet actually improved the patient's general well-being. This is particularly true in cases 1 and 22.

This regimen also eliminates the need for ammonium chloride, since the need for a substance to maintain serum chloride levels is eliminated, and the intrinsic value of ammonium chloride as a diuretic is somewhat controversial. Ammonium chloride may at times cause toxic symptoms.[14]

Medical literature has contained numerous articles over the past decade dealing with a disturbance, electrolyte imbalance, that is largely produced by a type of therapy designed to relieve another illness, congestive failure. Electrolyte imbalance may be termed hyponatremia, hypochloremia, dilution hyponatremia, etc. However, in most instances, this group of electrolyte disturbances results from attempts to change the natural saline environment of body cells. Since salt may be ingested according to need,[15] it would appear prudent to permit the cardiac patient to adjust his salt intake as required by the stresses placed upon him.

The mercurial diuretics are safe and effective. For maximum efficiency, parenteral administration is necessary, and the fact that injections are given at intervals may result in gradual fluid accumulation between injections. Although mercurial diuretics will continue to occupy a prominent place in cardiac therapy, they will undoubtedly be partially replaced by chlorothiazide.[16] It is, as Ford and his colleagues[17,18] and Laragh *et al.*[19] have demonstrated, the most effective oral diuretic. The reason for this is obvious. Chlorothiazide removes both sodium and chloride as well as water and is not inactivated by the gastrointestinal tract. The concomitant use of salt by the patient counteracts overly vigorous therapy and at the same time prevents loss of diuretic activity due to depleted sodium chloride levels. It may also prevent secondary hypokalemia.

CONCLUSIONS

Twenty-three cases of congestive failure have been presented which have been managed with digitalis, chlorothiazide, mercurial injections when needed, and a free salt diet. Twenty-two patients have been well controlled on this regimen. In no instance has intractable failure appeared and in 15 patients with BUN determinations, there have been no signs of renal insufficiency.

Patients appreciate the greater freedom in dietary intake they now enjoy. It is the author's feeling that restriction of sodium in the management of this syndrome is ineffective, except in the mildest cases, and that its continued use is superfluous with the diuretics now available. It is also postulated that this regimen will eliminate many electrolyte disturbances now encountered in congestive heart failure.

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The Low-Salt Syndromes in Congestive Heart Failure*

ALFRED VOGL, M.D., F.A.C.C.
New York, New York

NINE years ago Schroeder reported on a condition which he had observed in patients treated intensively for congestive heart failure. He described it as characterized clinically by rapid physical and mental deterioration and unresponsiveness to mercurial diuretics, and biochemically by a fall in serum chloride and increasing azotemia. He named this condition the low-salt syndrome.

Reports on similar occurrences by various investigators appeared in rapid succession and created the impression of the existence of an important, fairly well defined iatrogenic disorder that called for the close attention of the medical profession. These publications coincided with a period punctuated by two events: the rising popularity of salt-free diets and a vogue of a diuretic routine which employed prolonged series of daily mercurial injections in the treatment of congestive heart failure.

Appropriate measures for the correction of this "low-salt syndrome" appeared self-evident: as salt depletion was regarded the cause of the trouble, the administration of salt in a sufficient quantity seemed to be the logical remedy to reestablish physiologic electrolyte concentrations and thereby restore the response to mercurials.

With wider experience, however, it became clear that the original interpretation of the nature of the low-salt syndrome had been oversimplified and was applicable to a limited number of cases only, and that the therapeutic measures based on that concept proved effective only in relatively few patients. Moreover, attempts to replenish the presumably depleted salt stores often not only proved to be futile but were actually followed by an aggravation of congestive failure. Furthermore, the lowering of serum electrolyte concentrations, hyponatremia in particular, has been recognized as a *biochemical phenomenon that can occur spontaneously in protracted illness* under a variety of circumstances and as the outcome of different pathogenetic events.

Electrolyte Depletion in Congestive Failure

With the aid of flame photometry and of radioisotope technics, the following facts became evident:

A fall in serum chloride does not necessarily indicate a corresponding drop in serum sodium concentration. In fact, pathologic states are not uncommon in which the serum *chloride* level is lowered relatively more than that of sodium (hypochloremia), or in which the serum *sodium* concentration is depressed out of proportion to that of the chloride (hyponatremia).

In addition, it has been demonstrated through isotope technics that in congestive heart failure lowering of the electrolyte concentrations in the serum *does not as a rule signify depletion of the total body stores* of the respective solute. On the contrary, the total body sodium in decompensated cardiacs has been found markedly higher than in the normal (e.g. 65 meq/kg of sodium in congestive failure, 41 meq/kg in nonedematous subjects) and simultaneous determination of total body water revealed that the quantity of sodium retained in edematous patients was in excess of the retained volume of water. In patients with low serum sodium concentrations this excess quantity of sodium cannot possibly be present in the hypotonic extracellular fluid. It must therefore be assumed that sodium has

* From the Third Medical Division of Bellevue Hospital, and the Department of Medicine, New York University College of Medicine, New York, N. Y.

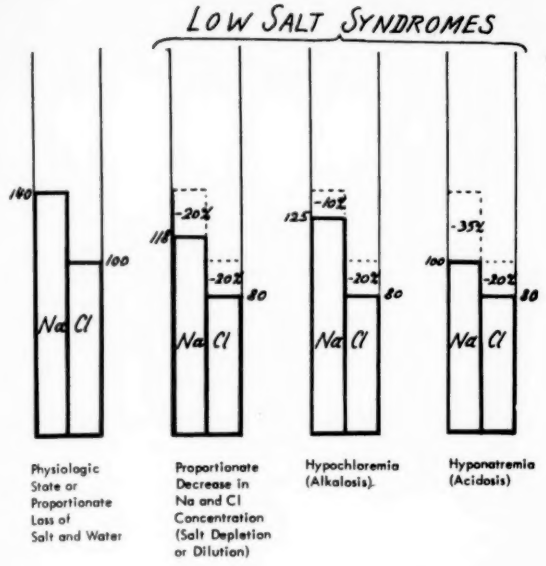

Fig. 1. Typical electrolyte patterns encountered in chronic congestive heart failure.

moved partly into the (potassium depleted and overhydrated) cellular elements. Another part of the sodium appears to have entered solid depots (bone, cartilage, connective tissue) or has become bound to polyelectronic constituents, such as mucoproteins. In such cases the lowering of the serum sodium concentration is obviously not the result of a real sodium deficiency but is due to dilution of the sodium in the extracellular fluid, a state therefore commonly referred to as *dilution hyponatremia.*

The diagram (Fig. 1) shows *four typical patterns* of serum sodium and chloride concentrations as encountered in patients in congestive heart failure:

(1) *Sodium and Chloride Concentrations within the Normal Range:* This pattern is seen in treated patients in whom loss of water and of electrolytes from the extracellular fluid has occurred in their physiologic proportions.

(2) *Proportionate Fall in Both Sodium and Chloride Concentration:* Example: a 20 per cent decrease of the concentration of both, resulting in a sodium concentration of 118 meq/*l* and a chloride concentration of 80 meq/*l*.

(3) *Predominant Fall in Chloride Concentration:* Example: a 10 per cent decrease in sodium concentration, resulting in a level of 125 meq/*l*, with a 20 per cent decrease in chloride concentration, resulting in a chloride level of 80 meq/*l*.

(4) *Predominant Fall in Sodium Concentration:* Example: a 35 per cent decrease in sodium concentration, resulting in a level of 100 meq/*l*, with a 20 per cent decrease in chloride concentration, resulting in a level of 80 meq/*l*.

Loss of electrolytes in excess of loss of water can produce patterns exemplified by the columns at the right. The same figures will, however, result from dilution of these electrolytes, or from a combination of both factors. Which one of these conditions prevails in a given case could be decided beyond question only by a concurrent estimation of the total body water and the total body electrolytes.

It seems, however, permissible to infer from currently available data, that in patients in whom edema coexists with hyponatremia this is probably the result of electrolyte dilution. Conversely, in cardiac patients who have lost their edema rapidly during vigorous diuretic treatment, the development of hyponatremia (and of a low-salt syndrome) is in all likelihood chiefly due to true electrolyte depletion.

Under these circumstances it is understandable, that it has been suggested to abandon the term "low-salt syndrome" altogether as being both inaccurate and misleading. After all, the salt stores of the body are admittedly not low in most of the cases, and no relationship has clearly been established between the biochemical findings and any well-defined clinical syndrome. However, it may be claimed in favor of the continued, though temporary, retention of the name that it has served as a useful catchword which dramatically brought into focus the dire consequences of an overenthusiastic but uncritical use of potent diuretic agents. Until more precise names are introduced which are based on a convincing correlation of clinical pictures with certain electrolyte changes, the term "low-salt syndromes" may still serve a useful purpose as a collective designation for a group of clinical and biochemical complexes.

Types of "Low-Salt Syndromes:" Among the syndromes encountered in congestive failure which are associated with lowered serum electrolytes, two main types have to be kept apart for practical purposes:

(1) An acute or subacute form developing during intensive diuretic treatment;

(2) A chronic form occurring in untreated as well as in treated patients, therefore evidently not attributable to excessive diuresis.

The Acute Low-Salt Syndrome

The *acute "low-salt syndrome,"* when appearing in the course of a vigorous diuretic regimen, may manifest itself predominantly as *dehydration*, as *hyponatremia* or as *hypochloremia*. It may develop immediately after the first profuse diuresis or only later after a series of copious therapeutic diureses. The symptomatology of the three types is not distinctive enough to permit a differentiation on clinical grounds. The more severe cases are marked by thirst, anorexia, nausea, striking prostration and lethargy, calf muscle cramps, a fall in blood pressure and a tendency to syncope in the erect position. Oliguria and some degree of renal failure frequently ensue.

(1) *Acute dehydration* after a *single* excessive diuresis usually results when a full dose of a mercurial is given either to a patient with little or no edema or to an edematous patient who is exceptionally sensitive to the diuretic action of the mercurial. Multiple, very painful muscle cramps are often the most distressing symptom. In elderly people the sudden increase in blood viscosity may cause arterial or venous thrombosis.

As long as water and solutes are lost in the proportions in which they exist in the extracellular fluid, serum electrolyte determinations will not reveal any definite deviations from the normal. The rise in hematocrit and plasma proteins, however, will give an indication of the changes that have taken place.

If the patient has adequate extravascular fluid stores a shift of fluid from the interstitial into the intravascular space will soon re-establish a more physiologic plasma volume and plasma concentration. In the more severely dehydrated patient, however, oral administration of salt and water (e.g., in the form of bouillon) is usually sufficient. Parenteral saline administration is required in emergency situations only or for patients who are unable to take fluids by mouth.

Alterations in the serum electrolyte concentrations attributable to diuretic therapy are more likely to be found after days or weeks of continued vigorous treatment. The clinical picture accompanying these biochemical changes has no distinctive diagnostic features and can easily be misinterpreted as being due to the anticipated down-hill course of advanced congestive failure. The cessation of a previously satisfactory response to mercurial diuretic may, of course, also be part of this inevitable development; it should, however, always arouse the suspicion of a possible disturbance of electrolyte distribution as a causative factor for this refractory state. Laboratory tests may then reveal either a predominant reduction in serum chloride concentration or a depression of sodium as well as chloride levels, sometimes affecting the sodium more than the chloride.

(2) *Hypochloremia* is more common as a side effect of prolonged mercurial treatment than hyponatremia since chloride loss consistently exceeds sodium loss during mercurial diuresis. Hence chloride depletion is virtually bound to develop whenever a patient whose salt intake is sharply restricted, receives mercurial diuretics frequently or even daily, and continues to respond to them. Since the chloride excreted in excess of sodium during mercurial diuresis requires the excretion of other cations, some degree of potassium depletion invariably accompanies the development of hypochloremia. The potassium deficiency does not necessarily reveal itself in a depression of the potassium concentrations in the serum (i.e., hypokalemia), as it affects predominantly the cellular potassium concentration.

(3) *Hyponatremia* is less likely to be produced by intensive diuretic therapy, unless the prevailing trend towards hypochloremia is effectively counteracted by ammonium chloride medication. Hyponatremia is frequently associated with varying degrees of acidosis, either because of the predominant depression of the fixed base or because of the supervening renal failure. It is very doubtful whether any case of hyponatremia complicating congestive failure can be ascribed exclusively to therapeutically caused electrolyte depletion. In fact, it is now known that in many cases of this kind there is no real lack of sodium but just dilution of it in an excess of extracellular water. Such patients, although

they may have excreted large quantities of electrolyte during diuresis, evidently have not lost a corresponding amount of water from the extracellular compartment.

The combination of salt restriction with a liberal fluid intake may well contribute to the development of hypotonicity of the extracellular fluid. However, in many of the patients in whom hyponatremia is discovered in the course of diuretic treatment, it has probably been present even before the institution of the diuretic regimen. In other words, hyponatremia found following excessive diuresis is most likely the result of acute electrolyte depletion superimposed upon a mild, pre-existent, long standing "dilution hyponatremia."

Chronic Dilution Hyponatremia

Hyponatremia apparently develops not rarely in connection with advanced congestive heart failure. It is a disorder of electrolyte and water distribution which is now known to occur also in other protracted wasting diseases, in malnutrition and in severe chronic infections. Its nature is not well understood. It appears, however, that the disorder begins with a disturbance of cellular metabolism which leads to the liberation of water, the loss of potassium, and a corresponding fall in cellular osmolarity. This, in turn, induces a shift of sodium into the cells and an adjustment of the extracellular fluid to the hypotonicity of the intracellular contents. This adjustment requires retention of water and necessarily results in an expansion of the total body fluid volume. The creation and maintenance of such a new and relatively stable condition of the body fluids involves changes in homeostasis and evidently requires modifications in the volume-controlling mechanisms and the osmoreceptor regulations of the body.

Experimentally it is possible to produce typical "dilution hyponatremia" in patients in congestive failure by administering long-acting pitressin preparations. This suggests that activation of ADH, the pituitary antidiuretic hormone, may play a major role in the causation of this disorder.

For two reasons the clinician is interested in this particular condition:

(1) The presence of hyponatremia connotes serious illness requiring well-planned efforts towards treating not only the basic cardiocirculatory disorder, but also possible complications, such as malnutrition or infections.

(2) The finding of lowered serum sodium levels might be misconstrued as a therapeutic indication for replenishing the apparent sodium deficit. In cases of "chronic dilution hyponatremia," such attempts would inevitably lead to further expansion of the extracellular fluid and to aggravation of the congestive failure, possibly with acute pulmonary edema.

Management of the "Low-Salt Syndromes"

What should be the attitude of the practitioner when encountering electrolyte disturbances in chronic congestive heart failure?

A correct assessment of such a situation is greatly facilitated by the routine determination of serum electrolytes *prior* to the institution of a diuretic regimen. At least in those patients who are likely to require intensive and/or prolonged diuretic treatment, an estimation of sodium, chloride, potassium, bicarbonates, urea nitrogen, and hematocrit should be obtained at the outset. Secured at this stage, this information will aid in evaluating the severity of the disease and the role of complicating factors. More important still, it will materially help to avoid uncertainty and errors in management later on, if and when attempts to establish cardiac compensation and to produce diuresis should encounter unexpected difficulties. It will then be easier to decide to what extent excessive diuresis may have been responsible for the development of the state of refractoriness.

Treatment of Dilution Hyponatremia: Chronic dilution hyponatremia is not known to produce any characteristic symptoms. It represents a laboratory finding encountered with increasing frequency as electrolyte estimations are done more routinely. Since specific measures aimed at the correction of the chemical changes as such are not available, therapeutic efforts will be limited to the best possible management of the underlying illness and of complicating disorders. Any plan of treatment should, however, invariably include the following rules: (1) Continuation of salt restriction; (2) limitation of

the fluid intake to about 1,200 cc/day; (3) administration of ammonium chloride and of potassium (or of potassium chloride) in order to increase the chloride stores and to counteract the ever-present cellular potassium deficiency; (4) administration of mercurials or other potent diuretics at intervals sufficiently long to permit homeostatic adaptations during the interim.

Production of Hyperchloremic Acidosis: A special method has been devised by Rubin *et al.* for the management of refractory cases of this type. It starts with the production of a hyperchloremic acidosis by administration of large doses of ammonium chloride and acetazolamide (Diamox). When a high serum chloride concentration has been produced, a series of mercurial injections is given while ammonium chloride administration is being continued. If this procedure results in satisfactory diuresis, the urine produced contains chloride far in excess to sodium. The net effect is diminution of total body fluid with a relative rise in the concentration of the serum sodium.

Cortisone: In certain cases of intractable congestive failure a course of cortisone has been employed as a means of reviving responsiveness to mercurials. It is conceivable that this method may benefit patients with dilution hyponatremia by initiating a rise in serum sodium concentration and thus creating a more favorable milieu for mercurial action.

Correction of Potassium Deficiency: The therapeutic measures discussed are apparently of little lasting effect unless proper consideration is given to the correction of the potassium deficiency which seems to be a basic element in the pathogenesis of dilution hyponatremia. Administration of potassium (5 to 6 g potassium chloride a day) may not only promote restoration of cellular osmolarity but also induce the return of sodium from the cells into the extracellular space. Thus the pathologic process is reversed with which the chain of events started which had led to hypotonicity of the extracellular fluid. For the reasons already discussed, the administration of sodium chloride is clearly contraindicated in the dilution type of hyponatremia.

Treatment of Electrolyte Depletion: In contrast to the uncertainties and difficulties with which the management of chronic *dilution* hyponatremia is beset, treatment of those conditions in which salt *depletion* is the essential causative factor, is much more promising. Furnishing the deficient electrolyte in adequate amounts is likely to succeed in relieving the clinical symptoms, in improving the chemical situation, and in restoring an adequate response to diuretics. To this end serial electrolyte determinations at the start and repeatedly during the course of treatment are indispensable since it is impossible to identify the type of disorder present or to gauge the progress on clinical grounds alone.

Hypochloremic Acidosis: The best results can be expected when the "low-salt syndrome" proves to be associated with hypochloremic acidosis. Ammonium chloride is the drug of choice to supply the deficient chloride. Oral doses of 4 to 8 g are usually adequate for the purpose and, in general, well tolerated. The administration of the drug in gelatine capsules ensures better absorption than in enteric-coated tablets. If oral intake appears inadvisable or impossible, slow intravenous infusions of a 1 or 2 per cent solution in 5 per cent glucose are indicated. Not more than 4 g of ammonium chloride per hour or 10 g/day should be given by vein in order not to overtax the detoxifying capacity of the liver upon which the conversion of the liberated ammonia into urea depends. These doses should be repeated until the serum chloride level approaches normal. While, as a rule, diuresis does not set in spontaneously at this point, the injection of a mercurial which was ineffective before is now likely to produce a satisfactory diuresis.

Hyponatremia: When hyponatremia is present, and either the clinical course or serial electrolyte determinations suggest that dietary sodium deprivation combined with a significant sodium loss plays a major causative role in the respective case, an attempt should be made to replenish the apparently depleted sodium stores. It will be indicated especially if the hyponatremia is associated with acidosis. Hypertonic solutions of sodium chloride or lactate (usually 5 per cent) are used for this purpose. The amount of sodium needed to raise the existent sodium level to normal can be calculated by a formula which takes the estimated total body fluid into consideration. Such calculations are, however, for

several reasons not of much practical value. In the first place, administration of sodium to a patient with hyponatremia is always to be regarded as an experiment with an unpredictable outcome. It is therefore clearly inadvisable to administer the total calculated quantity of sodium at one time. Moreover, clinical improvement and restoration of the response to mercurials has been found to occur before the serum sodium concentration had reached a normal level. It is therefore probably wise to give not more than 200 to 300 cc of 5 per cent saline per day by slow intravenous drip while restricting oral fluid intake sharply. The result should be evaluated by determining serum sodium levels from day to day as well as by watching the body weight, the urine output and, last but not least, the entire clinical picture. If no progress is made or if signs of increasing congestive failure develop, the experiment must be considered a failure and discontinued promptly.

In hyponatremia as well as in hypochloremia, however, success appears to depend on the continued adherence to a limited fluid intake and, to a considerable extent, on simultaneous potassium medication. Potassium should be given routinely in such cases, in alkalosis preferably as potassium chloride and in acidosis as a mixture of potassium citrate, acetate, and bicarbonate in fruit juices. In hyponatremia of uncertain etiology it may be advisable to start treatment with the administration of potassium alone. If this measure by itself, after a fair trial, does not succeed in raising the serum sodium concentration or improving the clinical picture, cautious administration of small quantities of hypertonic saline should be the next step.

Summary

The current concept of the "low-salt syndromes" and their management may be summarized as follows:

(1) The low-salt syndrome is not an entity either clinically or biochemically but represents a group of loosely related disorders.

(2) The finding of a low concentration of sodium and chloride in the serum can connote either electrolyte loss or water retention.

(3) The differentiation between these two states is made largely on clinical grounds. In most cases there is probably a combination of both factors.

(4) The principles of management are different for the depletion and the dilution types, but in a given case treatment remains largely empirical and must be guided by clinical as well as by laboratory observation.

(5) Correction of the altered electrolyte concentrations is more likely to be achieved if treatment is not limited to furnishing sodium and chloride but includes the restriction of fluid intake and the concurrent administration of potassium.

(6) The iatrogenic production of a "low-salt syndrome" is not an inevitable risk whenever a low-salt diet and potent diuretics are employed. It can, by and large, be avoided if treatment is individualized, and if the effect of the diuretic procedures is critically evaluated from day to day.

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Studies in Antihypertensive Therapy

Treatment of Hypertension in the Ambulatory Patient*

JOHN H. MOYER, M.D., F.A.C.C. *and* JOHN BEEM, M.D.

Philadelphia, Pennsylvania

IN THIS presentation, hypertension will be considered from the vascular dynamic viewpoint, giving primary attention to the effect of blood pressure reduction. It is well established that essential hypertension is associated with vascular changes in the brain, the heart, and the kidneys. Usually the kidneys are the first of the organ systems to show functional alterations and diffuse vascular damage from hypertension. It is difficult to evaluate cerebral function, unless cerebral deterioration is very advanced. It is also quite difficult to measure altered cardiac function. However, we can measure the functional capacity of the kidney by determining glomerular filtration rate and renal blood flow. Furthermore, pathologic tissue studies indicate that changes in the heart and brain usually parallel the kidney changes. When treating hypertension, we make the assumption that blood pressure reduction will arrest or at least slow up the development of these changes. In the latter part of this presentation, we shall present some observations to support this contention.

PATHOGENESIS OF HYPERTENSIVE DISEASE

In normal regulation of blood pressure, there are vasoregulatory centers in the brain which transmit impulses to the sympathetic nerves (Fig. 1). Many stimuli affect these centers such as emotional stimuli, cerebral stimuli, and circulating agents, notably circulating agents from the adrenals and other endocrine glands. Many investigators also think that the actions of hypertensive substances of renal origin are actually mediated through the brain, rather than having a direct effect on blood vessels. The sympathetic nervous system is then stimulated and sends impulses to the blood vessels causing arteriolar constriction. It has not been established whether the blood vessels react abnormally to normal stimuli, or whether an abnormal number of stimuli reach the blood vessels causing them to constrict, and thus produce hypertension. Many investigators believe that it is actually an increased number of vasoconstrictor impulses traveling over the sympathetic nerves which causes blood pressure elevation. When the blood pressure is elevated for a prolonged period of time, secondary changes are produced within the blood vessels which make them hyperactive, thus maintaining severe vasospasm even in the absence of sympathetic overactivity. The vasospasm produces ischemia, anoxia, and tissue changes.

When an individual with hypertension is stimulated by anxiety and frustration produced by environmental situations, this sets up an increased outflow of vasoconstrictor impulses and creates a more or less vicious cycle. Whether psychic factors are of etiologic importance or not, it is quite apparent that after the syndrome has been established, the more frequently the patient breaks into this hypertensive cycle, the more he tends to maintain a sustained blood pressure elevation. From 15 to 20 million people in the United States develop diastolic hypertension.

* From the Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia.

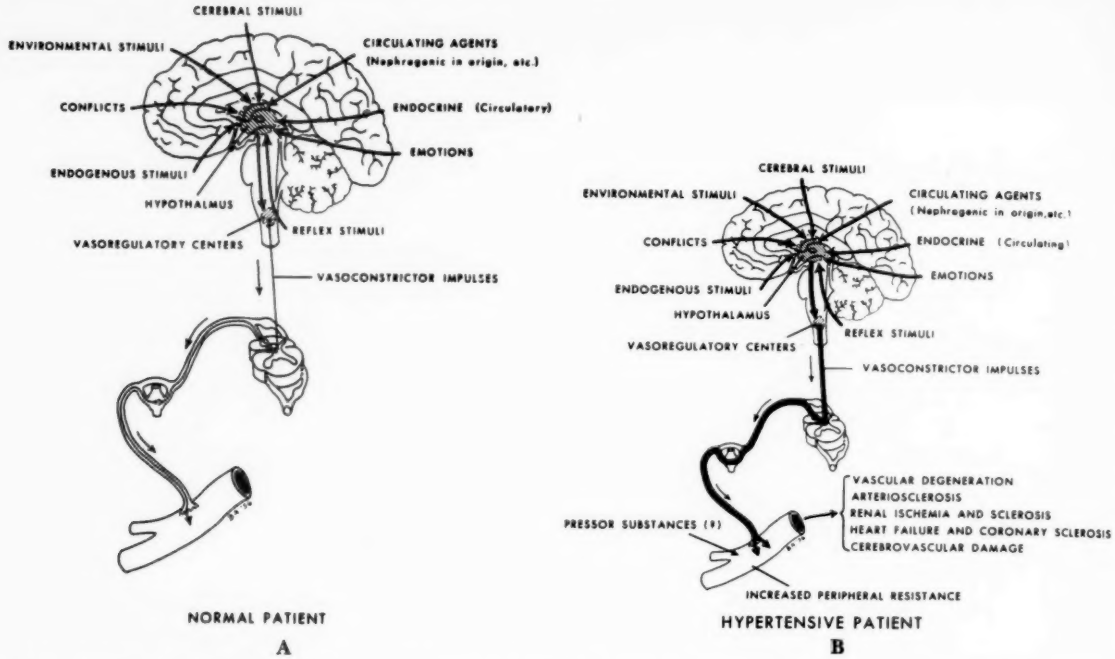

Fig. 1. Interplay of hereditary environmental and endogenous factors in hypertension. (A) Diagrammatic representation of blood pressure regulation through the sympathetic nervous system. (B) The patient with hypertension shows either an increase of vasoconstrictor impulses or an increased vascular response to normal impulses. This leads to blood pressure elevation and secondary vascular changes, particularly a more rapid progression of the arteriosclerotic process. (Adapted from Moyer *et al.*: *Am. J. M. Sc.* 230: 33, 1955.)

Renal Vascular Changes in Hypertension

What does blood pressure elevation alone do to the vascular system? The author and his associates studied 129 unselected patients with diastolic hypertension of all grades of severity who came into the hypertension outpatient clinic. They were a representative group of patients who could have walked into any physician's office, or into any hospital or clinic. Prior to therapy, glomerular filtration rates were determined on each patient. The observations are summarized in Figure 2 where the mean arterial blood pressure is plotted against the glomerular filtration rate. Normal glomerular filtration rate is 100 cc/min or more. The graph indicates that the greater the mean blood pressure in this group of 129 individuals, the lower was the glomerular filtration rate, indicating that the higher the blood pressure the more the kidneys were damaged. When the mean arterial blood pressure was below 130 mm Hg, there was no evidence of significant damage. But in the patients who had higher elevations, as for example, 180 mm Hg mean arterial blood pressure, the glomerular filtration rate was reduced significantly.

Figure 3 summarizes renal functional data in a patient who had malignant hypertension* and who was studied repeatedly before 1952, at which time there was no way of treating these patients effectively. This patient was followed for 10 months. Initially the glomerular filtration rate was 90 cc/min and the renal blood flow about 950 cc/min. Observations were made every two months, and the progressive reduction of glomerular filtration and gradual deterioration of renal function are apparent. After eight months, the patient developed uremia, and two months later he died. This is the typical course of untreated malignant hypertension.

It now appears that patients with severe hypertension but without papilledema will show the same progressive vascular degenerative

* Malignant hypertension in our studies has three criteria: (1) a diastolic blood pressure elevation which is marked, (2) papilledema, and (3) retinal hemorrhages.

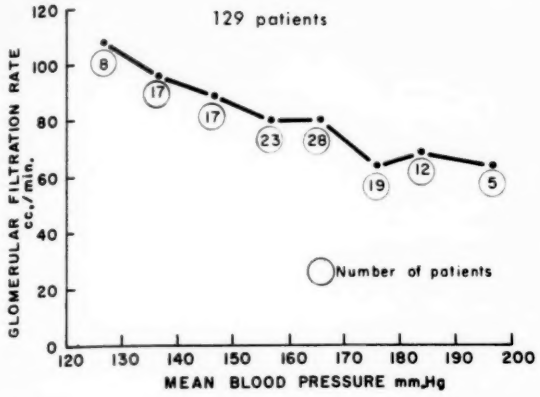

Fig. 2. The average values for glomerular filtration rate compared to increasing severity of hypertension as estimated by mean blood pressure. There is a greater reduction in glomerular filtration rate in those patients who show the greatest increase in blood pressure, thus indicating a direct relationship between the severity of the hypertension and the renal vascular deterioration. (Reproduced from Moyer *et al.*: *Am. J. Med.* 14: 164, 1958.)

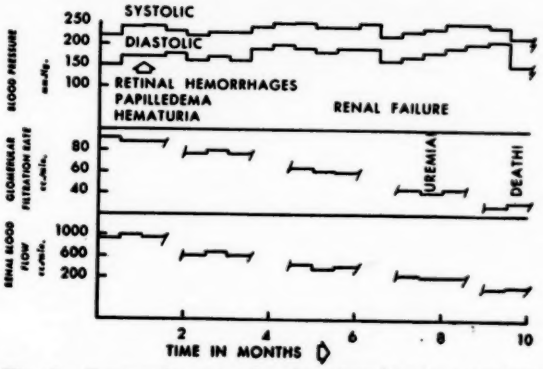

Fig. 3. Progressive vascular deterioration in a patient (J. J.) with malignant hypertension who was not treated. (Reproduced from Moyer *et al.*: *Am. J. Med.* 14: 177, 1958.)

changes when not treated (Fig. 4), as those seen in patients with malignant hypertension.

Drugs which lower blood pressure by depression of the sympathetic nervous system arrest these vascular changes. There are a number of things that will make sympathetic depressant drugs more effective. One of these is to try to keep the patient's environment as constant as possible and to remove the things to which he reacts most violently. Regular habits are important. Second, the physical status of the patient should be maintained in as good a condition as possible; and third, the patient's sodium intake should be kept as low as possible. However, when the patient psychologically reacts adversely to a low sodium diet, then he would do better by taking a diuretic (natriuretic) agent for depleting the body sodium.

Specific Therapeutic Considerations

Low Sodium Diet: When treating hypertension with drugs it is important to give consideration first to the intake and the excretion rate of salt. There seems little doubt that increased salt in-

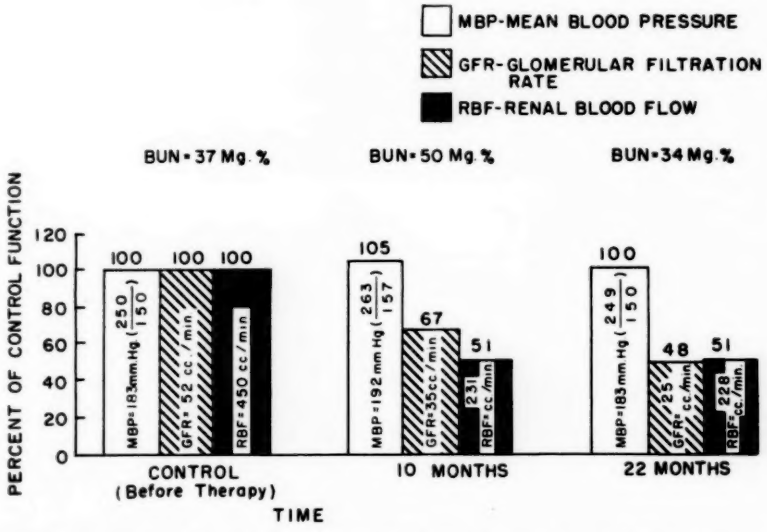

Fig. 4. Effect of severe hypertension (nonmalignant) on renal function over a period of two years in a patient (R. L.) not treated. This patient did not have papilledema. (Reproduced from Moyer *et al.*: *Am. J. Med.* 14: 177, 1958.)

TABLE I

Evidence Implicating Salt in Hypertension

A. Diminished salt intake counteracts hypertension.
   1. Blood pressure in essential hypertension reduced.
      L. Ambard and E. Beaujard, 1904 and 1905; R. Laufler, 1904; C. Lowenstein, 1907; F. Allen, 1920 and 1922; F. Volhard, 1931; W. Kempner, 1944; A. Grollman, 1945; and J. M. Bryant and E. Blika, 1947.
   2. Blood pressure in renal hypertension reduced.
      C. Lowenstein, 1907.
   3. Symptomatic improvement in hypertension.
      F. Allen, 1920 and 1922; and W. Kempner, 1944.
   4. Improves some patients with malignant hypertension.
      W. Kempner, 1944.
   5. Improves hypertension and other effects of toxemia of pregnancy.
      K. DeSnoo, 1937.
   6. Augments antihypertensive action of sympathectomy.
      J. M. Bryant and E. Blika, 1947.

B. Increased salt intake intensifies hypertension.
   1. In the presence of renal disease and congestive failure.
      L. Ambard and E. Beaujard, 1904 and 1905.
   2. In essential hypertension.
      R. Bayer, 1907; W. Addison, 1928; I. McQuarrie, 1935; and G. E. Perera and D. W. Blood, 1947.
   3. Produces experimental hypertension with DOCA
      H. Selye, 1943.
   4. Increases pressor response to DOCA in human beings.
      G. A. Perera and D. W. Blood, 1947.
   5. Potentiates pressor response to DOCA in experimental nephritic rats.
      A. I. Knowlton *et al.*, 1947.
   6. Statistical correlation between salt intake and incidence of hypertension.
      Lewis K. Dahl and R. A. Love, 1954 and 1957.
   7. Possible correlation of increased salt intake and hypertension in natives of Bahamas.
      M. Moser, 1957.

C. Increased salt elimination counteracts hypertension.
   1. Cation exchange resins decrease gastrointestinal sodium absorption and blood pressure.
      W. Dock, 1946.
   2. Hypertensives in congestive failure often highly resistant to antihypertensive therapy. Control of congestive failure frequently restores responsiveness to vasodepressors.
   3. Increased environmental temperature, physical exercise, diarrhea, vomiting, etc., intensify response to antihypertensive therapy.
   4. Antihypertensive action of chlorothiazide in patients with or *without* congestive failure.

TABLE II

Limitations of Salt Restriction or Depletion Therapy in Hypertension

A. Must be severe and is difficult to achieve in most patients.
   A. Grollman *et al.*, 1945; and W. Kempner, 1955.

B. Limited efficacy.
   1. Modest improvement fails to justify the means in most patients.
      G. A. Perera, 1947.
   2. Effective only in presence of adrenal malfunction.
      H. Schroeder *et al.*, 1949.
   3. Fails to reduce blood pressure in malignant hypertension.
      G. A. Perera, 1955.
   4. General limitations of efficacy, etc.
      J. Musser, 1920; J. McLester, 1922; S. Strouse, 1921; J. O'Hare and W. Walker, 1923; H. Mosenthal and J. Short, 1927; S. Berger and M. Fineberg, 1929; and others.

C. Produces fluid and electrolyte imbalances.
   1. Salt deprivation syndrome.
      D. L. Edsal, 1909; J. H. Talbott, 1935; H. Schroeder, 1949; and W. Kempner, 1955.
   2. Negative K and Na balance, acidosis, hypocalcemia, digitalis intoxication.
      W. Kempner, 1955, and others.
   3. Azotemia and uremia, often requiring salt replacement.
      F. M. Allen and J. W. Sherrill, 1922; and others.

take aggravates the hypertensive state (Table I). Likewise depleting body stores of sodium by a very low sodium intake will result in a reduction in blood pressure and improvement of symptoms in patients with hypertension (Table I). Therefore, even though salt may not be an important factor in the etiology of hypertension, it certainly becomes of utmost importance in therapy.

The use of a low sodium diet is of limited therapeutic usefulness (Table II), since these diets are quite unpalatable and the blood pressure response is erratic. Of greater practical importance is the observation that depleting body sodium by increasing elimination with diuretic (natriuretic) agents increases the effectiveness of antihypertensive drugs which depress the sympathetic nervous system.

Mercurial Diuretics: Mercurial diuretics are moderately effective (Fig. 5) when used properly but they must either be given orally or parenterally. Parenteral use requires a frequency

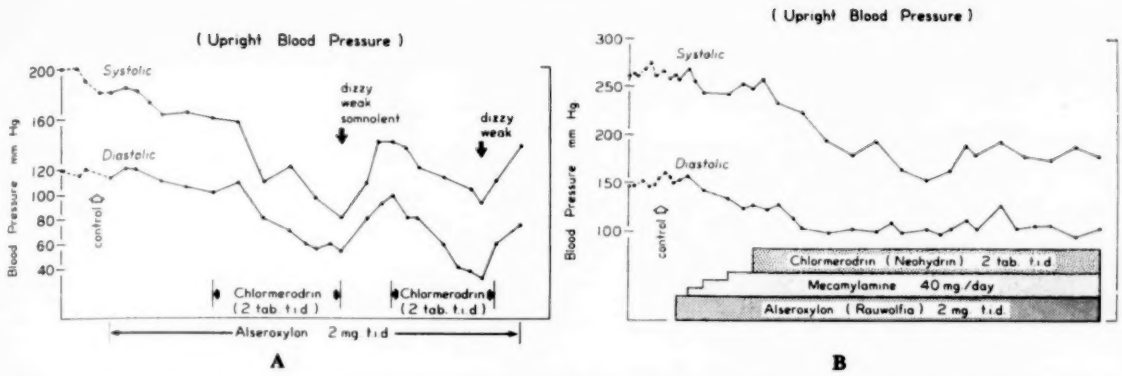

Fig. 5. Effect of oral mercurial on blood pressure response of other drugs. (A) When chlormerodrin (Neohydrin) was given to this patient with hypertension who was receiving rauwolfia (alseroxylon fraction) there was a significant enhancement of the blood pressure lowering effect of the rauwolfia. (B) Additional reduction in blood pressure is observed when chlormerodrin was given to a patient who was receiving rauwolfia and the ganglionic blocking agent mecamylamine (Inversine). (Reproduced from Heider, Dennis, and Moyer: *Ann. N. Y. Acad. Sc.* 71: 456, 1958.)

which limits their practical applicability. A normal individual who takes a dose of a mercurial diuretic parenterally, and is not in heart failure, will show a good increase in sodium excretion during the first 12 hours but during the second 12 hours, he will retain salt (Fig. 6). At the end of 36 to 48 hours, he has excreted about the same amount that he would have excreted if he had not received the diuretic. But when this same patient is given meralluride (Mercuhydrin) in a dose of 2 cc every 12 hours, sodium excretion increases and the action of the antihypertensive drugs will be increased as the sodium excretion goes up. This has exactly the same effect as a very low sodium intake. More recently some drugs have become available which are equally as potent given orally as meralluride given parenterally. The most outstanding of these is chlorothiazide (Diuril).

Chlorothiazide: Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiozine-1,1-dioxide) is an orally effective natriuretic agent. Electrolyte

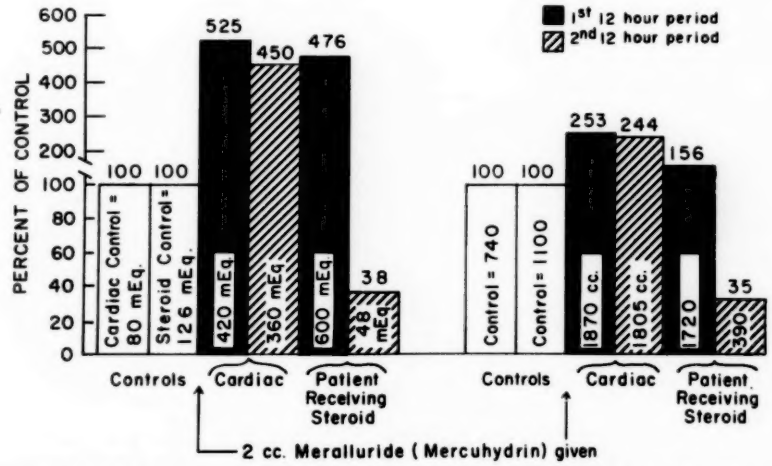

Fig. 6. Comparison of the effect of a parenterally administered mercurial diuretic (Mercuhydrin) on sodium and water excretion in a patient who had sodium and water retention due to steroid (prednisone) administration and one who had retention due to cardiac failure. The bar graphs on the left summarize the effects on sodium excretion; on the right, water excretion. After 12 hours in the patient with heart failure there was continuing diuresis whereas in the patient with "steroid edema" there was retention of sodium and water so that the excretion rate actually fell below that observed during the control period. The patient with hypertension responds similarly to the patient with steroid edema. This demonstrates the necessity of giving parenterally administered mercurial diuretics more frequently in these patients when enhancement of the blood pressure lowering effect is to be anticipated.

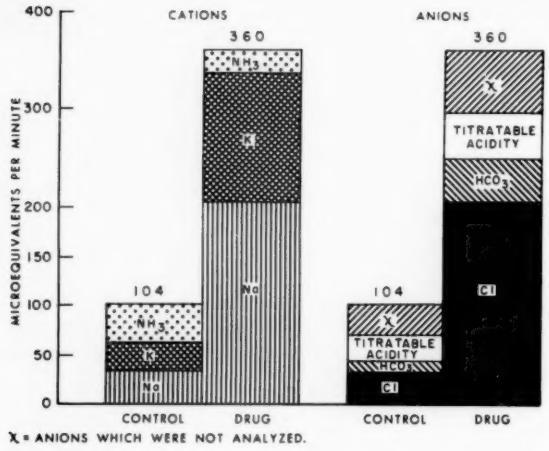

Fig. 7. Electrolyte excretion pattern following 2,000 mg of chlorothiazide given orally. The primary effect is an increase in sodium and chloride excretion with lesser effects on potassium and bicarbonate. (Reproduced from Moyer *et al.: Proc. Soc. Exper. Biol. & Med.* 95: 529, 1957.)

excretion studies indicate that the predominant influence is on the renal excretion of sodium and chloride (Fig. 7) with a smaller effect on the excretion of potassium and bicarbonate in the presence of an alkaline urine.

Upon oral administration, the onset of action is within two hours and the duration of action is approximately 6 to 12 hours. It is repeatedly effective on continuous daily or twice daily administration. Oral doses are more effective for increasing the total 24-hour excretion of sodium than are rapidly excreted intravenous doses.

Comparative potency of chlorothiazide and other currently available diuretic agents indicate that a dose of approximately 500 mg of chlorothiazide is roughly equivalent to four tablets (40 mg) of chlormerodrin (Neohydrin) in ability to augment sodium excretion and is roughly twice as potent as acetazolamide (Diamox). A dose of slightly more than 1,100 mg of chlorothiazide (oral) is equivalent to 1 cc of meralluride (Mercuhydrin) administered intramuscularly. When used in the treatment of hypertension chlorothiazide should be given in a dose of 500 mg twice a day.

Figure 8 is the response in a patient who was treated with a blocking agent plus rauwolfia. The blood pressure came down, but not adequately. Chlorothiazide was then added to the

TABLE III

Summary of Effect of Chlorothiazide Given to 48 Patients with Hypertension Who Were Previously Poorly Controlled on Combined Rauwolfia and Mecamylamine Therapy

Age:	34 to 56 (average—49)
Sex:	Male—14
	Female—34
Race:	Negro—42
	White—6
Rauwolfia dosage—kept constant	
Average dose of mecamylamine—reduced by approximately one-half	
Duration of therapy—6 to 12 months	
Number responsive*—39	
Inadequate response—9	
Mean blood pressure reduction—26%	
Weight loss—1.6 to 5.2 lb	

* Blood pressure reduced greater than 20 mm Hg.

therapy which produced a marked natriuresis and diuresis. There was an additional reduction in blood pressure even at half the dose of the ganglionic blocking agent. When the chlorothiazide was discontinued, the blood pressure increased again. As long as the drug produces natriuresis, it markedly enhances the effect of the ganglionic blocking agent (Table III) as well as the rauwolfia compounds.

When the patient requires a large dose of the ganglionic blocking agent to begin with, he usually requires some of it after the chlorothiazide is added even though the dose is reduced. Figure 9 shows a patient who was getting mecamylamine (Inversine) plus reserpine. The blood pressure responded when chlorothiazide was added with a marked reduction in blood pressure even though the dose of the ganglionic blocking agent was reduced to half. However, when the ganglionic blocking agent was discontinued entirely, the blood pressure increased. Here again, *it is the combination of drugs that is effective, and one drug alone is not adequate.*

Table III summarizes observations on 48 patients who received chlorothiazide in combination with rauwolfia and mecamylamine. After receiving mecamylamine, the over-all dose in 48 patients was 37 mg. After chlorothiazide was added, the dose of mecamylamine was reduced to 17 mg, whereas the blood pressure remained about the same or decreased further. In other

words, a greater degree of blood pressure regulation was obtained with half the dose of mecamylamine. Thirty-nine out of the 48 patients responded in this fashion.

It is of some importance that chlorothiazide produces a marked increase in sodium excretion and in chloride excretion and only temporarily increases potassium excretion. This is different from the carbonic anhydrase inhibitors such as acetazolamide (Diamox) which produce a marked increase in bicarbonate excretion, as well as in sodium and potassium excretion. Another important aspect is that a continued natriuretic response follows daily oral administration of chlorothiazide. Side effects associated with the use of chlorothiazide are listed in Table IV.

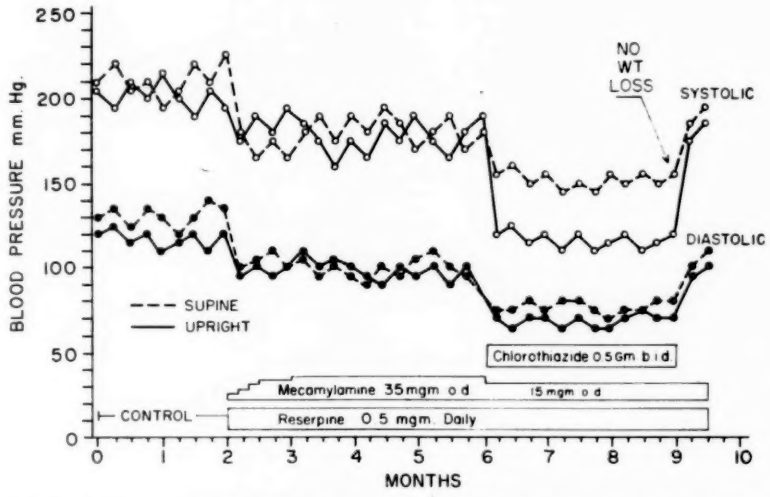

Fig. 8. Potentiating effect of chlorothiazide on the blood pressure response to reserpine and the ganglionic blocking agent, mecamylamine. The additional reduction in blood pressure was observed despite a reduction in the dose of mecamylamine of more than 50 per cent. When the chlorothiazide was discontinued, the hypotensive effect was lost and it became necessary to raise the dose of mecamylamine again. (Reproduced from Heider, Dennis, and Moyer: *Ann. N. Y. Acad. Sc.* 71: 456, 1958.)

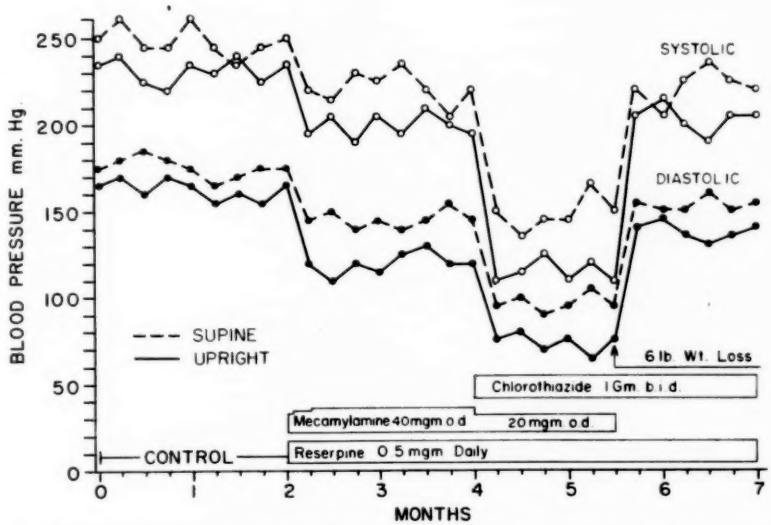

Fig. 9. Potentiation of mecamylamine by the administration of chlorothiazide in a 39-year-old male with grade 3 eyeground changes, ECG findings of left ventricular strain, BUN 20 mg, and no congestive failure. Even though the dose of mecamylamine was decreased, it was not possible to discontinue the drug entirely without losing the control of the blood pressure. (Reproduced from Heider, Dennis, and Moyer: *Ann. N. Y. Acad. Sc.* 71: 456, 1958.)

TABLE IV
Side Reactions to Chlorothiazide

Reaction	Incidence	Remarks
Gastrointestinal side effects Anorexia Nausea Vomiting Epigastric burning	11%	When this occurred relief was frequently obtained by discontinuing the drug for 24 to 48 hours
Skin rash	1.5%	
Weakness	22%	
Muscle cramps	5%	Observed only in patients with concurrent heart failure and marked edema
Paresthesias	1 case	
Electrolyte imbalances		
Serum K	Minimum 3.8 meq/L Mean reduction 0.5 meq/L	No clinical symptomatology observed
Serum sodium, chloride, bicarbonate, BUN	No significant changes	
Electrocardiogram	No significant changes	No clinical evidence of hypokalemia observed in authors' patients

In summary we have observed that the increase in sodium excretion produced by drugs such as chlorothiazide makes the antihypertensive agents more effective, so that very frequently a reduction in blood pressure following rauwolfia is observed in patients who would not be responsive to rauwolfia alone. In patients who require ganglionic blocking agents, a response is obtained with a much smaller dose of the blocking agent when chlorothiazide is given concurrently, and therefore fewer side effects are observed. In these patients who require only small doses of the blocking agent when given alone, the blocking agent can often be discontinued completely when chlorothiazide is given concurrently. Finally the natriuretic effect of this drug continues with daily administration. By contrast the carbonic anhydrase inhibitors lose their effect within three days on continued administration so that an interrupted dosage schedule must be used. This characteristic makes them useless for treating hypertension.

Using this information it seems appropriate to draw up an over-all treatment schedule for the antihypertensive agents (Table V). Therapy should be instituted with chlorothiazide. After one week, rauwolfia should be added to the therapeutic program. When this is not adequate, more potent agents should be added as described subsequently.

RAUWOLFIA

Of the various rauwolfia preparations, there is very little difference in the blood pressure response to alseroxylon, reserpine, rescinnamine, deserpidine, or crude root. There is one difference in the rauwolfia compounds, and this has to do with the incidence of side effects. Those who have used these drugs to any extent are particularly annoyed by the washed out, fatigued, depressed feelings that these patients experience while taking reserpine. They get the same effect, but to a lesser extent with the alseroxylon fraction of rauwolfia (Rauwiloid) or the whole root (Raudixin), both of which contain multiple alkaloids.

Side Effects: The most serious side effect of the rauwolfia compounds is the agitated depression which is seen occasionally. The first symptom suggestive of agitated depression is insomnia in the early morning hours. Probably one-fifth of the patients who receive a rauwolfia preparation (especially reserpine) for a prolonged period experience this side effect at some time or other. This should be the "tip-off" to the therapist to be watchful because these are the patients who may

TABLE V
Over-all Therapeutic Program for the Treatment of Hypertension

Severity of hypertension	Initial therapy	Adjunctive therapy when not adequately responsive to initial therapy
Mild (diastolic pressure fixed at 100 but <120 and without complications)	Chlorothiazide (500 to 1,000 mg b.i.d.)	Rauwolfia alseroxylon—4 to 8 mg daily or whole root—100 to 200 mg daily or reserpine—0.25 to 0.5 mg daily
Moderately severe (diastolic >120 or <120 with complications due to hypertension)	Chlorothiazide and rauwolfia (dosage as outlined above).	Hydralazine—dose from 25 mg q.i.d. to a maximum of 400 mg daily. When hydralazine not effective—discontinue and use ganglionic blocking agent instead.
Severe hypertension (diastolic more than 140 or more than 120 with complications)	Chlorothiazide and rauwolfia (dosage as outlined above).	Ganglionic blocking agents. Dosage arrived at by titration procedure.

develop agitated depression. When the condition is progressive, the patient develops a sense of impending danger. He feels that a catastrophe is about to occur but he cannot describe it. These are the patients who may develop suicidal tendencies.

One might anticipate that these patients with agitation should respond to phenobarbital. Actually, they respond better to dextroamphetamine (Dexedrine). We have observed numerous patients who had been having difficulty sleeping because of rauwolfia. When they took 2.5 to 5 mg of Dexedrine they had a good night's sleep for the first time in days or weeks. The Dexedrine probably overrides the depressive state. It is quite likely that it is those patients who have tendencies toward depression who more frequently get depressive reactions when taking rauwolfia.

When a patient is unable to sleep in the early morning hours, this is not an absolute contraindication to the drug. This is an indication for the physician to become alert to a potential problem, and perhaps the therapist should discuss the potential problem with the patient's spouse, or discuss this frankly with the patient. If the symptoms progress to the point that the therapist thinks the patient is developing a panic state, this is an absolute indication to discontinue the drug. The side effect is nearly always reversible unless there is underlying psychiatric pathology, particularly in older people who might become depressed in any event. Some patients may require shock therapy. This will be the patient who was just hovering on the borderline of developing an acute psychiatric depression before he was given rauwolfia which precipitated the episode. This patient cannot be expected to recover until he receives appropriate therapy for his basic disease. Usually when the depression is caused by the drug *per se*, the process is readily reversible when the drug is discontinued.

RAUWOLFIA WITH HYDRALAZINE (APRESOLINE)

It is the opinion of the authors that hydralazine should not be used by itself because there is a very high incidence of side effects when this is done. When used in combination with rauwolfia the severity, as well as the incidence, of side effects are reduced considerably. When an adequate response is not observed after the patient has been receiving chlorothiazide (500 mg twice a day) and rauwolfia (alseroxylon 8 mg/day) for two weeks or more, then the dose of the rauwolfia should be reduced by half and hydralazine should be added, starting with a dose of 25 mg after each meal and at bedtime. At least four hours should be allowed between doses. The dose is increased weekly in 25 mg increments until an adequate reduction in blood pressure is

TABLE VI

Comparison of Blood Pressure Response to Mecamylamine When Given Orally and Parenterally (Mean Values For 11 Patients)

	Route of administration	
	Oral	Intramuscular
Control blood pressure (mm Hg)		
Upright		
Systolic	186	181
Diastolic	119	120
Supine		
Systolic	203	203
Diastolic	126	125
Blood pressure after drug		
Upright		
Systolic	122	118
Diastolic	81	82
Supine		
Systolic	165	160
Diastolic	98	97
Dose (mg)	19	20
Onset of action (min)	37	46
Duration of action (hr)	22	21

obtained or the side effects become prohibitive. The drug should not be continued in those patients who do not obtain a significant response. Not more than 400 mg/day should be given. When the drug is ineffective it should be abandoned in favor of ganglionic blocking agents when the hypertension is of adequate severity to warrant the use of these compounds.

GANGLIONIC BLOCKING AGENTS

The use of ganglionic blocking agents is difficult, but the data indicate that in a patient with hypertension, particularly at the beginning of the malignant phase, the outlook when not treated is no better than it is with carcinoma of the lung. Were an agent to become available which would increase the average survival time of a patient with carcinoma of the lung from seven months to three or four years, this would be acclaimed as a good therapeutic measure. The therapist can do just that in patients with malignant hypertension. Thus, treatment of severe hypertension with antihypertensive drugs is a good therapeutic measure. Even though difficult to use, probably the most effective measures in this area are the ganglionic blocking agents used in combination with chlorothiazide and rauwolfia.

Dose Titration: There are some specific problems associated with the use of ganglionic blocking agents. The first of these is effective dose titration, and it is our belief that this is where most therapists fall short. It is very important to start with a small dose of the ganglionic blocking agent, gradually increasing the dose until the standing blood pressure is reduced to the desired level, i.e., about 150/100. As a guide to determination of the proper dose, the therapist should use not only the blood pressure observations which he takes in the office, but he should also use symptomatology. For example, if the patient comes in to the office stating that he has attacks of dizziness at certain times during the day, this is adequate to indicate that he is getting excessive hypotension at that time. Using these symptoms plus the blood pressure observations, (using home blood pressures in some patients) the therapist can regulate the blood pressure quite effectively.

We prefer to use only one or two of the ganglionic blocking agents because it is like using digitalis; the therapist becomes more proficient with the use of one particular agent even though the pharmacologic properties of all of the preparations may be similar. Usually we use mecamylamine (Inversine) because it is completely absorbed, the responses to the drug orally and parenterally are the same (Table VI), and the response is more predictable. Some patients get excessive constipation and dry mouth with this compound. When this occurs pentolinium (Ansolysen) is used. In actual practice there is very little difference in effectiveness or in the incidence and severity of side effects among the different ganglionic blocking agents.

The patient should be given chlorothiazide and a rauwolfia preparation before starting the blocking agent. We use alseroxylon (Rauwiloid) or the crude root (Raudixin) as the rauwolfia preparation of choice, giving one tablet four times a day for two weeks and then reducing the dose to two tablets (or 4 mg) daily. The mecamylamine (Inversine) is then started using a dose of 2.5 mg at breakfast and supper, followed by giving a daily lunch dose of 2.5 mg.

After one week, the daily lunch dose is gradually increased, then the breakfast dose is increased at weekly intervals. The supper dose is increased less rapidly or not at all. Because the drug action lasts a long period of time, the biggest dose is given in the morning and at lunch, for when the patients are relaxed at night they do not need nearly so much drug. When the patients receive too large a dose at supper, they experience excessive hypotension when they get up in the morning.

One of the rauwolfia compounds is used in combination with the blocking agents because this combination of drugs not only blocks the sympathetic nervous system in the brain and at the ganglia simultaneously but in addition the patient gets sedation and tranquility from the rauwolfia compound. The chlorothiazide when given simultaneously increases sodium elimination which makes the blood vessels less responsive to vasoconstrictor impulses.

The Problem of Constipation: This is an ever-present problem with ganglionic blocking agents because not only do the drugs block the sympathetic ganglia but they also block the parasympathetic ganglia which results in constipation. The therapist must be very vigilant against constipation and use cathartics freely. The cathartic of choice is a matter of trial and error. We find that cascara is the best. There is a good standardized compound available in tablet form, i.e., Dorbane. It appears to be the best one in tablet form that we have used so far. Many patients prefer the elixir of cascara sagrada in a dose of 10 to 30 cc. It should be used freely and in considerably larger doses than ordinarily used in practice. Some patients who do not do well with cathartics may do much better with Prostigmine in a dose of 15 to 30 mg taken about an hour before breakfast. On the other hand, other patients get rather severe cramps with Prostigmine and do better with the cathartics. By trial and error the therapist must find out which is the best for the individual patient. At the beginning of the treatment, it is difficult to arrive at the precise method of therapy for any one particular patient.

RENAL DAMAGE

In the patient who has depressed renal function due to advanced damage to his kidneys, the renal vessels do not dilate adequately when the blood pressure is reduced too rapidly or excessively because of the vascular spasticity. When the kidneys are already functioning poorly because of the vascular damage, bringing the blood pressure down may actually aggravate the existing renal failure. However, when the blood pressure is kept down for a prolonged period of time, the vascular degenerative changes are arrested. Therefore, in the patient who has an elevation of the BUN, the therapist should probably not reduce the blood pressure to normotensive levels immediately. After a month of blood pressure regulation, the blood pressure can be lowered to normal levels without functional depression. When the BUN is normal before treatment, the blood pressure can be reduced to within normotensive ranges immediately without concern.

If the blood urea nitrogen is 30 to 60 mg %, usually the standing blood pressure can be reduced to about 170 mm Hg systolic and 110 diastolic without experiencing difficulty. When the BUN is 60 to 100 mg %, the blood pressure should not be reduced much below 190/120 initially. When the pressure is regulated at this level for two to four weeks, it can be decreased gradually to normotensive levels without further aggravating the renal failure. When the pretreatment BUN is more than 100, blood pressure reduction is useless unless the patient has heart failure which is another problem. The mortality in our patients when the blood urea nitrogen was above 100 mg % was 100 per cent, and we have not benefited the patient by reducing the blood pressure, again indicating that the patient should be treated before he has gone beyond the point of no return.

ENVIRONMENTAL FACTORS

Treating the patient with hypertension is like treating the patient with diabetes. When the patient who has diabetes is given a constant dose of insulin and then allowed to vary his carbohydrate intake, his urinary sugar varies also. Similarly, when antihypertensive drugs are used, nervous impulses are being blocked at a constant level by a fixed amount of the drug. Figure 10 summarizes observations made on an insurance

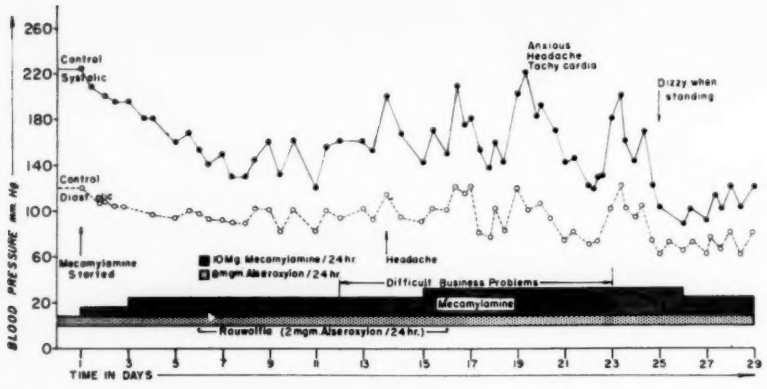

Fig. 10. Periods of stress increase the dose requirement of ganglionic blocking agents. This is the blood pressure response in a patient who was becoming well regulated with a combination of rauwolfia plus mecamylamine (Inversine). However, when the patient was subjected to excessive stress, he developed marked fluctuations in blood pressure and increased symptomatology. It became necessary to increase the dose of the ganglionic blocking agent to control the blood pressure. However, when the stress was removed, the dose of the blocking agent proved to be excessive, resulting in hypotension. When the dose of the drug was then reduced, the patient's blood pressure was well regulated again. (Reproduced from Moyer *et al.*: *A.M.A. Arch. Int. Med.* 98: 187, 1956.)

executive. He was fairly well regulated until he attended a series of executive board meetings. He became very tense during board meetings and his sympathetic nervous system was stimulated, resulting in more than the usual number of impulses emanating over the sympathetic nervous system to the arterioles. This was reflected in a variable blood pressure. The dose of the ganglionic blocking agent was increased but the blood pressure continued to fluctuate. He then developed some tachycardia and angina, whereupon he was advised to discontinue work and accept a less strenuous position. The blood pressure then stabilized. This indicates that the therapist continues to deal with a human individual whose sympathetic nervous system is connected to a brain which overresponds to environmental stimuli. Unless the therapist finds means and methods for stabilizing his patient's emotions as far as his reactions to his environment are concerned, he will have a pretty difficult problem regulating doses of the drugs. So, again, there are very definite limitations to the drug therapy of hypertension.

HYPERTENSIVE EMERGENCIES

When patients present themselves with a hypertensive emergency, the therapist must consider bringing the blood pressure under control rapidly. Probably the most effective agents for this purpose are reserpine and rescinnamine. The average dose of rescinnamine is about 10 mg and the average dose of reserpine is 5 mg given intramuscularly. Rescinnamine is just as effective as reserpine, except that twice as large a dose must be given.

The treatment of the hypertensive crisis is to give 2.5 mg of reserpine intramuscularly as a trial dose, repeated in two hours. If this is not adequate 5 mg every six hours should be tried. A 10 mg dose may be tried when a dose of 5 mg is not adequate. If the patient does not respond to this we usually try a ganglionic blocking

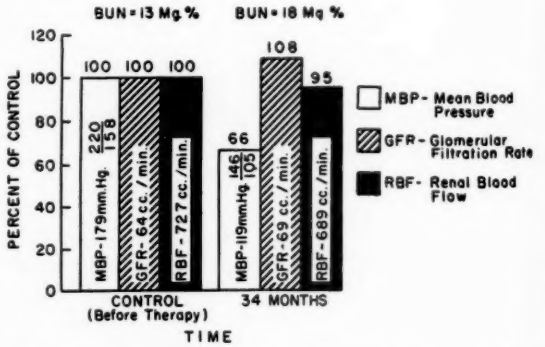

Fig. 11. The response to therapy in a patient who showed moderate renal damage prior to the administration of antihypertensive drugs. After three years of therapy, renal function was not reduced from the pretreatment values, suggesting that the vascular deteriorating effect of hypertension had been arrested. (Reproduced from Moyer *et al.*: *Am. J. Med.* 24: 177, 1958.)

agent given parenterally. We prefer hexamethonium subcutaneously starting with a dose of 15 mg and doubling it every two hours until an adequate response is obtained or a maximum of 50 mg is employed. If the patient does not respond to this dose, we use parenteral veratrum, preferably alkavervir (Veriloid) or protoveratrine (Veralba).

Vascular Response to Blood Pressure Reduction

What evidence is there that blood pressure reduction arrests vascular changes associated with hypertension? Let us refer to a group of patients with nonmalignant hypertension that we have followed for three to five years. Some have been treated, others have not. As a general rule, the untreated patients were not treated because either they lived out of the city or they elected not to return to the clinic because it was inconvenient to come to the hospital.

Observations in Nonmalignant Hypertension: Figure 4 summarizes observations made on a patient who did not have malignant hypertension and was not treated. Comparing the blood pressure 10 months later, note that it was about the same as it was during the control period. His glomerular filtration rate was only 67 per cent of the control value and the renal blood flow was 51 per cent. Compare this patient with the one in Figure 11. The latter is a typical response in the treated patient. After three years, the blood pressure was reduced from 220/158 to 146/105. The glomerular filtration rate was 108 per cent of control value and the renal blood flow 95 per cent. This indicates that with blood pressure reduction the vascular changes that occur in the kidney due to hypertension have been arrested. It also shows that renal function did not improve. Thus, when the blood pressure was controlled in these patients, renal function did not return to normal but the vascular damage was arrested at the stage of vascular change existing at the time therapy was instituted.

Figure 12 summarizes observations made on a group of patients with diastolic blood pressure above 130 mm Hg and another group with diastolic pressure more than 100 but less than 130 mm Hg. Compare the glomerular filtration rate in the treated patients with the untreated ones with more severe disease and it will be seen that the glomerular filtration rate for the treated patients three years later was about the same as prior to treatment, while in the untreated patients the glomerular filtration rate was now about 65 per cent of control values. This shows that in untreated patients with severe nonmalignant diastolic hypertension above 130 mm Hg, a definite progressive vascular deterioration, as estimated by glomerular filtration rate, is seen. This applies equally to the renal blood flow (Fig. 12 B).

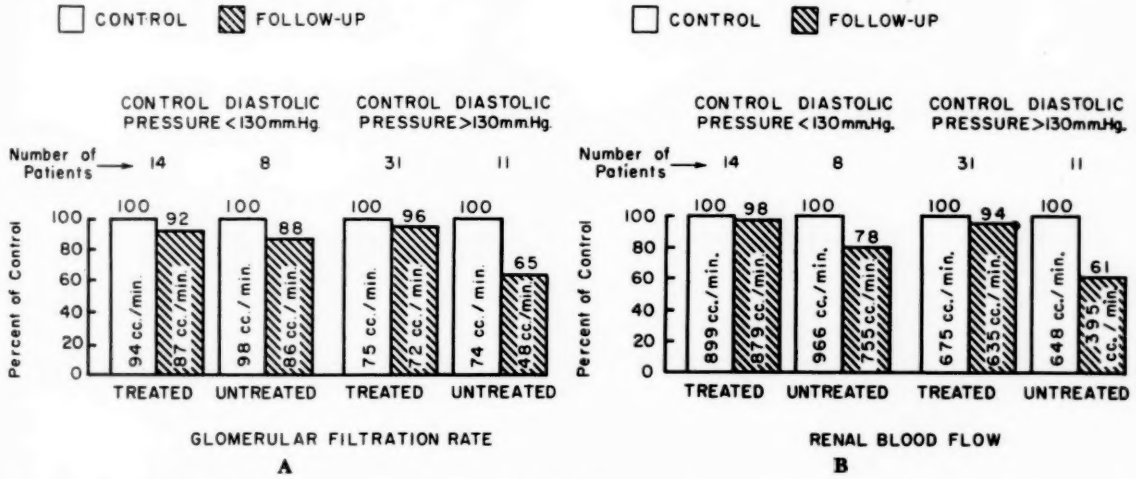

Fig. 12. Comparison of renal function tests in treated and untreated patients with hypertension. (A) Glomerular filtration rate used as an index of renal damage. (B) Same comparison using renal blood flow as the index of renal damage. (Reproduced from Moyer *et al.*: *Am. J. Med.* 24: 177, 1958.)

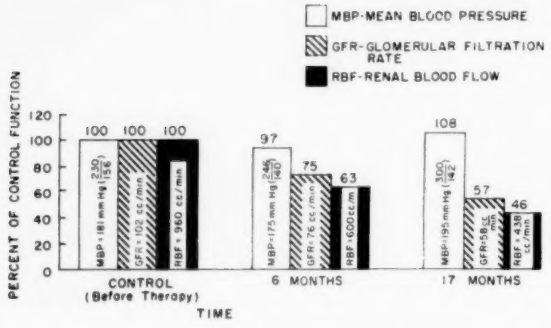

Fig. 13. Renal function in a 38-year-old patient with malignant hypertension who was not treated with antihypertensive drugs. There was a progressive reduction in glomerular filtration rate and renal blood flow. The patient died several weeks after the last renal function test was completed.

Observations in Malignant Hypertension: In malignant hypertension, the same type of progressive vascular deterioration occurred as was observed in severe nonmalignant hypertension. Figure 13 is a typical case of an untreated patient and it shows that after 6 months without therapy there was a decrease in the renal blood flow and glomerular filtration rate. After 17 months, they decreased even further.

Figure 14A and B show typical results in a treated patient with malignant hypertension. Under treatment, the blood pressure was controlled at approximately 158/110. There was no evidence of further reduction of glomerular filtration rate, and four years later it was the same as it was prior to treatment. So here also we have a patient with malignant hypertension, who before treatment showed about a 60 per cent reduction in renal function. As he has been followed along for four years, it is apparent that the vascular changes were arrested so that even though the renal function was reduced by half prior to therapy, it now remains exactly the same as it was prior to treatment.

When the glomerular filtration rate was used as an index of renal damage for a group of 21 patients with malignant hypertension, it stayed exactly the same for the patients who received treatment, whereas in the untreated group the average glomerular filtration rate dropped from 70 to 44 cc/min, showing that the kidneys deteriorated in these patients and uremia ensued. This indicates that reduction in blood pressure can arrest the vascular changes associated with malignant hypertension. The average follow-up was only 10 months in the untreated patients because most of the patients died in that period of time, while the treated patients have been followed in excess of three years.

Mortality data indicate that of 31 patients (including the 21 on whom follow-up differential renal function studies were obtained) with malignant hypertension, 13 were treated and 18 were untreated. In 18 that were untreated, only 1 patient is living and 17 have died, while in the treated patients, 11 are living and 2 are dead.

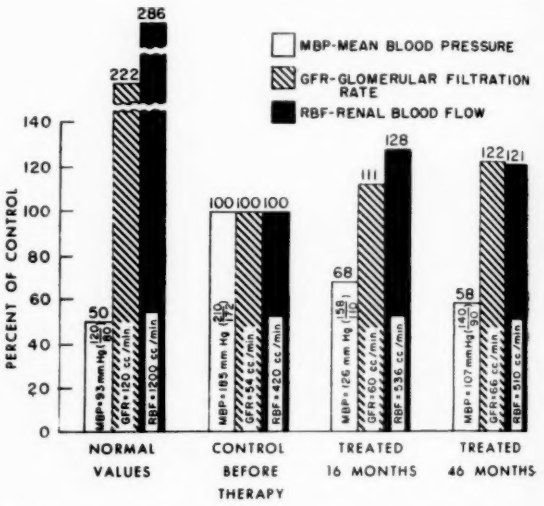

Fig. 14A. Summary of results in a patient with malignant hypertension who was treated effectively with a combination of rauwolfia and a ganglionic blocking agent. Prior to institution of therapy glomerular filtration rate and renal blood flow were reduced to approximately 50 per cent of normal due to the vascular deterioration associated with malignant hypertension. Following effective antihypertensive therapy for a period of four years, there was no further reduction in glomerular filtration rate and renal blood flow, indicating that the vascular deterioration had been arrested by effective therapy. (Reproduced from Moyer *et al.*: *Am. J. Med.* 24: 177, 1958.)

The follow-up period in the treated group is now over three years for all patients. The average follow-up period in the untreated group was only 14 months because of the early death of the patients.

It is interesting that of the untreated patients, 11 out of the 18 actually died of renal failure and uremia. Treatment of patients with malignant hypertension has completely altered the cause of

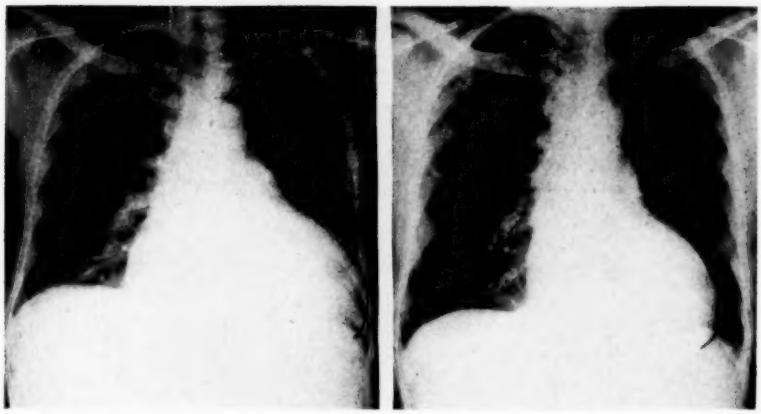

Fig. 14B. Reduction in heart size as the blood pressure was controlled in this same patient. (Reproduced from Moyer *et al.*: *Am. J. Med.* 24: 177, 1958.)

death and when treatment was started prior to development of renal failure (as long as the BUN is normal) patients rarely died of renal failure. In untreated patients, two-thirds or more died of renal failure. When treated patients die the cause of death is usually a cerebrovascular accident or a coronary occlusion.

Summary

Blood pressure elevation of adequate severity and for a prolonged period of time will definitely produce vascular changes in the brain, the heart, and the kidneys. The more severe the hypertension, the more marked these changes will be in the kidneys. Effective reduction of blood pressure may completely arrest these vascular changes regardless of the method used for blood pressure reduction. Although the changes are arrested, renal function rarely returns to normal.

Hypertension aggravates and hastens the development of arteriosclerosis. Reducing the blood pressure arrests this hastening process, but still arteriosclerosis progresses just as it does in the normotensive individual.

The method of blood pressure reduction is probably not important, insofar as arresting the vascular changes associated with hypertension is concerned. The important thing is that the blood pressure be reduced effectively. This the surgeon can do, particularly when he employs concurrent medical therapy. We would concur with this approach just as long as the blood pressure is severe enough to warrant surgical therapy and the surgeon is proficient at doing sympathectomies. On the other hand, when the psychiatrist, or the general practitioner, or the internist who carries psychiatric overtones, can "talk the blood pressure down," this is good therapy. Unfortunately, being neither psychiatrist nor surgeon, we prefer to use drugs and our results using psychotherapy (and placebo) have been poor.

Any drug therapeutic program that is effective in bringing the blood pressure to a normal or relatively normal levels, is an effective therapeutic program. Generally speaking, our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as a background medication for all antihypertensive drugs. This is probably the most effective measure for blood pressure reduction. Then the sympathetic nervous system is blocked by different methods. The centrally acting drugs are used first. The most common ones are rauwolfia and hydralazine. Usually in milder cases rauwolfia is given an initial trial alone and if the patient needs additional therapy, he may receive hydralazine (Apresoline). In the moderately severe cases, we give a therapeutic trial of hydralazine with rauwolfia. For the more severe cases when the diastolic blood pressure is fixed above 120 to 130 mm Hg, we use ganglionic blocking agents, such as mecamylamine or pentolinium.

Chlorothiazide as an Adjunct in the Treatment of Essential Hypertension*

MARVIN MOSER, M.D., F.A.C.C. *and* ALICE I. MACAULAY, M.D.
Valhalla, New York

THE recent synthesis of an orally effective, potent diuretic agent, chlorothiazide[1] (Diuril), presented an opportunity to judge the effect of prolonged "salt depletion" on the course of the patient with essential hypertension without the necessity of employing drastic dietary restriction. During the past year 106 patients have been studied and treated with chlorothiazide alone and in combination with specific antihypertensive drugs in an effort to determine whether continuous diuretic therapy on a long-term basis is feasible and whether better blood pressure control can be achieved in this manner as compared to results obtained without a diuretic agent.[2]

Pharmacologic studies in animals and humans have revealed that chlorothiazide is a potent diuretic agent which produces a marked increase in the urinary excretion of sodium, potassium, and chloride.[3,4] No evidence of tolerance to drug action has developed on continued administration of this agent as compared to that which is noted after other orally effective diuretics such as the carbonic anhydrase inhibitors [acetazolamide (Diamox)]. The potency of chlorothiazide compares favorably with that of parenterally administered mercurials and is generally superior in its sodium-depleting effect to other presently available oral diuretic agents. Preliminary reports on the use of this agent alone and in combination with more specific antihypertensive drugs in the treatment of essential hypertension have been encouraging.[5,6] Side effects have been minimal and no specific "toxicity" has thus far been reported.

CASE MATERIAL AND METHOD

Preliminary observations in our clinic confirmed previously published reports that chlorothiazide, when utilized alone in doses of between 0.5 to 1.5 g a day in normotensive individuals, has little or no effect upon blood pressure. In an additional series of 15 patients chlorothiazide, when utilized alone, had a minimal effect on both systolic and diastolic blood pressures of hypertensive individuals who had previously been untreated and were on a normal diet (Table I). For this reason it was believed that chlorothiazide would be most effective as an antihypertensive drug when used with the more specific autonomic blocking agents, or in conjunction with a low sodium diet.

Chlorothiazide was added to the treatment regimen of 91 hypertensive individuals who had been followed for periods of from six months to four years. All of these patients had been on continuous therapy with one or a combination of two or more of the following: rauwolfia drugs, hydralazine (Apresoline), mecamylamine (Inversine), or a new ganglionic blocking agent, trimethidinium methosulfate, designated WY 1395.[7]

Patients were classified as follows with regard to the severity of their hypertensive disease: 22, Grade I or IA; 34, Grade II or IIA; 34, Grade III to IIIA; and 16, Grade IV, according to previously published criteria.[2] This classification takes into consideration fundu-

* From the Cardiac Clinic, Department of Medicine, Grasslands Hospital, Valhalla, N. Y. This study was supported by a grant-in-aid from the Merck Sharp & Dohme Laboratories, West Point, Pa.

TABLE I
Blood Pressure Response to Chlorothiazide

	Number of cases	Average blood pressure before addition of chlorothiazide*	Average blood pressure after addition of chlorothiazide†	Average blood pressure change
Chlorothiazide alone	15	174/108	159/100	−15/−8
Rauwolfia plus chlorothiazide	39	184/112	166/98	−18/−14
Hydralazine Reserpine plus chlorothiazide	17	170/102	156/94	−14/−8
Mecamylamine Hydralazine Reserpine plus chlorothiazide	35	174/101	154/85	−20/−16
Total	106			

* Represents blood pressure after prolonged therapy with drugs other than chlorothiazide.
† Average duration of therapy, 7 months.

scopic findings, as well as evidence of cardiac or renal disease, progression of symptoms, if any, and duration of the disease.

Thirty-five patients were receiving a ganglionic blocking agent. Dosage of chlorothiazide administered varied between 0.5 and 1.5 g daily given in two divided doses. Larger doses were given initially with reduction of dosage after the first week or two of treatment if blood pressure control was achieved. In patients with nitrogen retention chlorothiazide was started in doses of 0.25 g twice daily and reduced if azotemia increased. Patients were maintained on a normal diet with the exception that no salt was added to food. Intermittent evaluation of sodium excretion revealed that most patients were ingesting approximately 3 to 4 g of sodium chloride daily on this regimen.

Results

Effects on Blood Pressure

Results of average blood pressures on antihypertensive drugs alone and blood pressures after chlorothiazide was added to the treatment regimen are given in Table I. Most patients reported were maintained on chlorothiazide for from six months to one year. Some blood pressure reduction occurred in all groups, but the degree of lowering was significant only in those patients who had previously been on rauwolfia alone (reserpine or Raudixin) or on ganglionic blocking agents in combination with other drugs. It should be noted that blood pressure levels had already been lowered by therapy prior to the addition of chlorothiazide. In many cases the dosage of the ganglionic blocking agents had to be reduced significantly to avoid hypotension after chlorothiazide was added.

In 5 cases an attempt to withdraw ganglionic blocking drugs was made. In 3 patients a satisfactory blood pressure level was maintained by chlorothiazide alone, or in combination with reserpine (0.25 to 0.50 mg daily) or Raudixin (100 mg per day), and the more potent drugs were permanently discontinued. In two cases it was necessary to continue ganglionic blocking drugs. In several instances blood pressure control was achieved with chlorothiazide in combination with rauwolfia drugs in patients who ordinarily might have required intensive therapy with more potent drugs.

The potency of chlorothiazide as a blood pressure lowering agent was greater in several patients when they were maintained on low sodium intakes (under 1 g of sodium chloride daily). Results in this group of patients will be reported elsewhere.[8]

Case Histories

The following cases illustrate the use of chlorothiazide in combination with other drugs.

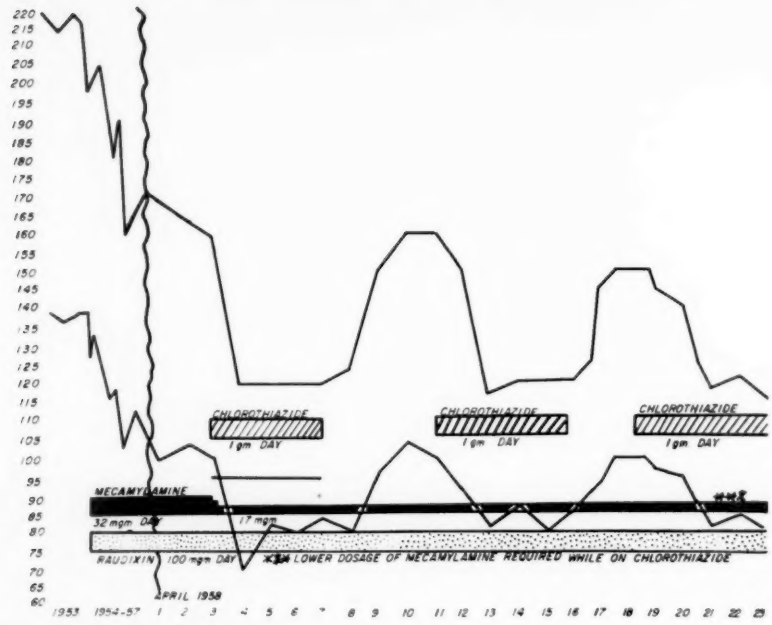

Fig. 1. Case 1. A 43-year-old man with severe essential hypertension. Excellent response of blood pressure to addition of chlorothiazide to mecamylamine-Raudixin regimen. Note prompt rise in blood pressure when chlorothiazide is withdrawn.

CASE 1. A 43-year-old white male who had been treated for severe essential hypertension for three years with ganglionic blocking drugs in combination with Raudixin had experienced a satisfactory drop in blood pressure, although normotensive levels had never been achieved. Figure 1 illustrates the results of the addition of chlorothiazide, 0.5 g twice daily, to treatment. Dosage of mecamylamine (Inversine) has been reduced from 32 mg daily to 17.5 mg since the addition of chlorothiazide. Side effects have decreased following this reduction of dosage. Note the rise in blood pressure within 36 hours after chlorothiazide is withdrawn and the fall in pressure within 24 to 36 hours after the drug is readministered (Fig. 1). Normotensive blood pressure levels have persisted on combination chlorothiazide-mecamylamine-rauwolfia therapy.

CASE 2. A 48-year-old white male with progressive hypertension had noted dyspnea on exertion for several weeks. Blood pressures varied between 220/140 and 250/160. On combination therapy with chlorothiazide, reserpine, and mecamylamine an excellent blood pressure and symptomatic response was noted within two to three days (Fig. 2). An attempt to control blood pressure without mecamylamine failed and combination therapy has now been continued with good results for six months.

OTHER EFFECTS OF CHLOROTHIAZIDE

A marked diuresis and weight loss of between two and three pounds were noted in all patients with few exceptions during the first three days of therapy with chlorothiazide. After that time, urinary output and weight usually stabilized. Six patients complained of nausea and a bitter taste in the mouth during the first month or so of treatment. Nausea disappeared after discontinuation of the drug. Postural hypotension was accentuated after chlorothiazide was added to the regimen of patients on ganglionic blocking agents. This, however, tended to disappear as the dosage of the blocking agent was reduced.

Serum Electrolyte Changes: In two patients with renal failure and a "salt losing" syndrome before the use of chlorothiazide, excessive loss of potassium and progressive nitrogen retention was noted after the drug was administered. In contrast, patients with normal or only slightly impaired renal function showed little change in serum sodium, potassium, and chloride levels on prolonged chlorothiazide administration. Some decrease in serum electrolytes was noted initially but these stabilized on continued therapy. For this reason, in patients who were able to maintain a reasonably good diet, supplemental potas-

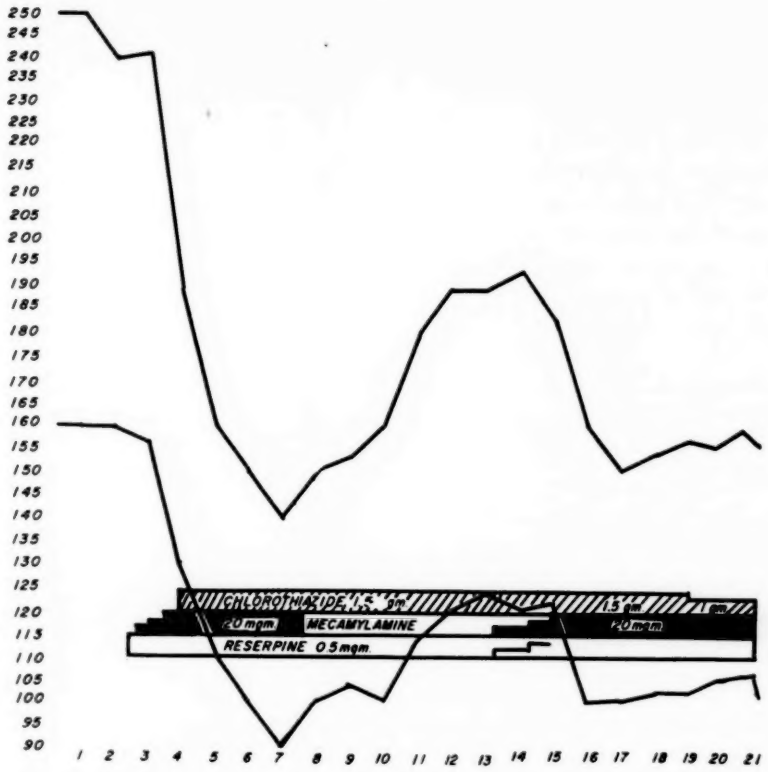

Fig. 2. Case 2. A 48-year-old man with grade III essential hypertension. Blood pressure control achieved only by combination of mecamylamine, reserpine, and chlorothiazide. Note blood pressure rise again after withdrawal of mecamylamine.

sium was not added to treatment after our initial experience. Extra orange juice and other foods rich in potassium were advised in all cases. In patients who were on poor diets 1 to 3 g of extra potassium were administered daily in the form of potassium chloride or Potassium Triplex. It may be assumed that a decrease in intracellular potassium could occur in patients on prolonged chlorothiazide therapy despite normal serum levels and/or lack of clinical symptoms of electrolyte depletion. Possible effects of this depletion upon renal tubular cells, especially in patients with renal disease, must be watched for.

Urinary retention occurred in several male patients in the 45 to 60 age group. None of these patients presented obvious evidence of prostatic hypertrophy.

No definite arrythmias could be attributed to the use of chlorothiazide in our group of patients.

Skin Rash: Three patients developed macular or petechial rashes while on chlorothiazide. Complete blood studies failed to reveal any hematologic abnormalities. Although these skin reactions could represent a "toxic" or "allergic" response to the drug, further observations to prove or disprove this association are necessary.

In the three diabetic hypertensive patients who received chlorothiazide for long periods of time no definite change was noted. Possible hyperglycemic effects of this agent are presently under investigation.

Discussion

It is apparent from these observations that chlorothiazide possesses a significant blood pressure lowering effect when combined with more specific antihypertensive agents. This effect occurs in a high percentage of cases and tolerance to drug effect has not been observed to date. The absence of significant side effects following the use of this drug and the fact that

other more potent agents with side reactions may be reduced in dosage without loss of clinical result when chlorothiazide is added to the treatment regimen suggest that this drug will be of value in the treatment of hypertensive patients in the moderately severe to severe group.

Marked restriction of salt would not appear to be necessary when chlorothiazide is used continuously. Best results are obtained when moderate sodium restriction is continued, allowing 2–4 g sodium daily. This allows for a palatable diet.

Dosage of chlorothiazide is standardized and does not require the persistent changing and adjustments necessary when ganglionic blocking agents and other antihypertensive drugs are used. It would appear from preliminary observations that 0.75 to 1 g a day is a satisfactory dose in most hypertensive individuals, although higher doses (1.5 g a day) may be necessary during the first week of treatment.

The antihypertensive action of chlorothiazide would appear to be the result of loss of salt and the resultant changes in blood volume, although other more specific antihypertensive actions may exist quite apart from its saluretic effect. Although low potassium levels have been reported following the continued use of chlorothiazide, especially in patients with renal disease and congestive heart failure, it has not been our experience to observe this in most cases of hypertensive cardiovascular disease without renal failure. Potassium levels should be carefully observed in all patients with renal disease and should be intermittently checked during the first two to three weeks of chlorothiazide treatment in all patients. We do not believe, at this time, that the addition of potassium to therapy is necessary, other than by dietary means, in most cases. Hypertensive patients on therapy are already taking a large number of pills and, if possible, additional medication should be avoided. If weakness occurs, or if potassium levels are noted to fall, the addition of potassium chloride by mouth (2 to 4 g daily in 4 divided doses) or Potassium Triplex (4 cc four times daily) will usually control symptoms or signs. Patients receiving digitalis and chlorothiazide should always be given potassium supplements.

Summary

(1) Chlorothiazide is a potent, orally effective nonmercurial diuretic which produces a continuous diuretic effect without significant side effects. Significant reduction in blood pressure in hypertensive individuals has not been noted with chlorothiazide alone in the majority of cases, but is frequently noted when the drug is combined with other antihypertensive drugs, such as the rauwolfia drugs, hydralazine, and the ganglionic blocking agents. Optimal doses range from 0.5 to 1.5 g daily in two divided doses.

(2) Nausea, weakness, electrolyte depletion, and skin rashes present the only side effects; these are only occasionally of significance. Severe electrolyte disturbances are noted, however, following chlorothiazide in patients with renal failure and those on low sodium diets. The drug should be used with care in patients with renal failure.

(3) The mode of action of chlorothiazide in hypertension most probably depends upon its ability to increase sodium excretion and reduce blood volume.

(4) It would appear that chlorothiazide represents an important advance in the modern treatment of the hypertensive patient. This drug would appear to potentiate the effects of other drugs. In many cases of severe disease it may be possible to substitute this "easily managed" compound for the more potent ganglionic blockers without loss of blood pressure lowering effect.

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The Use of Carbethoxysyringoyl Methylreserpate in Hypertension*

BENJAMIN BARBOUR, M.D., GEORGE IRWIN, M.D., HARRY YAMAHIRO, M.D., WALLACE FRASHER, M.D., *and* ROBERT F. MARONDE, M.D.

Los Angeles, California

CARBETHOXYSYRINGOYL methylreserpate (Ciba Su-3118†) is derived chemically from reserpine by hydrolysis to methylreserpate and re-esterification with carbethoxysyringoyl chloride. Its structural formula is shown in Figure 1.

PHARMACOLOGY

The pharmacologic actions of carbethoxysyringoyl methylreserpate may be summarized as follows:[1]

Cardiovascular Actions: In the dog anesthetized with pentobarbital, 1.0 mg/kg of the drug given intravenously caused an average decrease of 40–50 mm Hg in the mean arterial blood pressure. This hypotensive effect was gradual in onset over a period of two or three hours and was persistent in the acute experiment lasting about seven hours. A slowing of the heart rate of 15–20 per cent occurred. There was less tendency to potentiate the pressor effect of epinephrine than with reserpine.

The daily administration of 40 to 50 μg/kg for approximately ten days to unanesthetized normotensive dogs lowered the blood pressure 30 to 40 mm Hg.

In unanesthetized neurogenic hypertensive dogs, 10 to 15 μg/kg/day markedly reduced the pressor spikes and lability of blood pressure seen in such animals. A decrease in the heart rate of about 25 per cent was observed in these dogs.

Tranquilizing Actions: Following the intravenous administration of 2.0 mg/kg of carbethoxysyringoyl methylreserpate to the unanesthetized dog, tranquilization was noted and the effects corresponded to those seen after 0.25 mg/kg of reserpine. No tranquilization was observed after 1.0 mg/kg of intravenous carbethoxysyringoyl methylreserpate. Miosis, slight respiratory stimulation, and relaxation of the nictitating membrane were present at both dose levels of the newer drug.

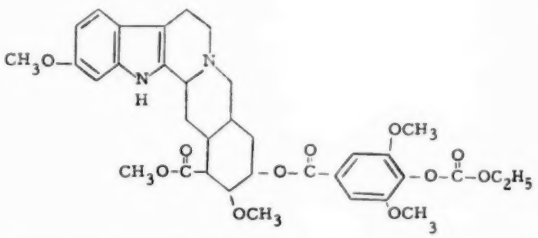

Fig. 1. Structural formula of carbethoxysyringoyl methylreserpate (Su-3118).

No tranquilization or other gross effects were noted in two monkeys given 600 μg/kg of intravenous carbethoxysyringoyl methylreserpate. Two other monkeys became well tranquilized after being given the same dose of reserpine.

Gastrointestinal Actions: Diarrhea did not occur in unanesthetized dogs during chronic administration until the dose of carbethoxysyringoyl methylreserpate reached 100 to 200 μg/kg/day. Under the same conditions, diarrhea is usually seen with reserpine in doses of 30 μg/kg/day.

* From the Hypertension Clinic of the Los Angeles County Hospital, and the Department of Medicine, College of the Medical Evangelists and University of Southern California School of Medicine.

† The authors are indebted to Mr. Louis Spiegel of Ciba Pharmaceutical Products Inc. for supplying the Su-3118, now designated as syrosingopine.

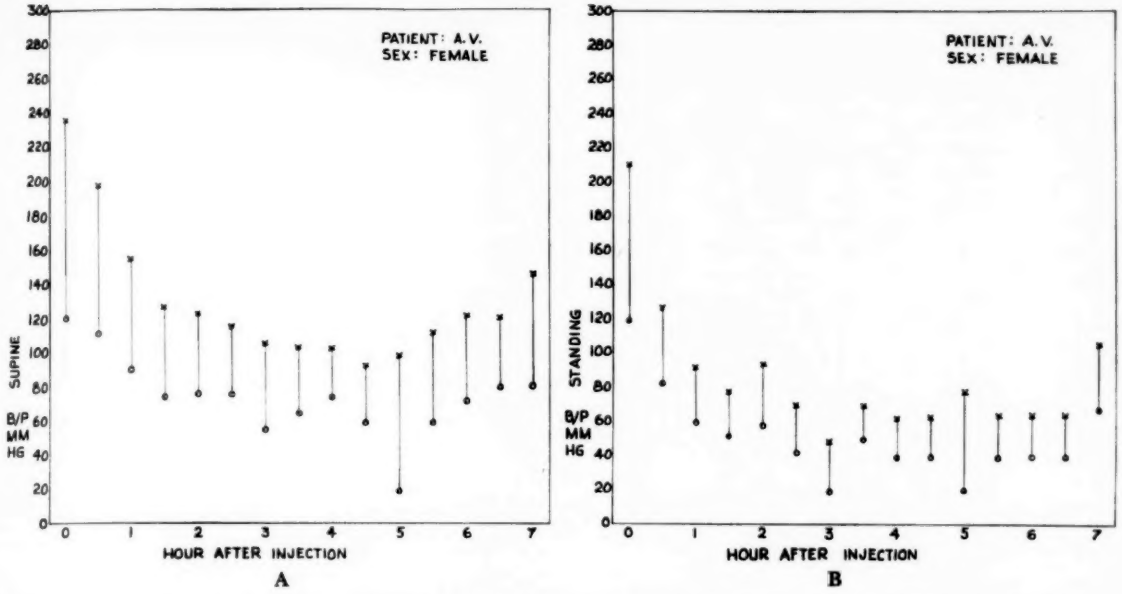

Fig. 2. Effect of 7.5 mg carbethoxysyringoyl methylreserpate (Su-3118) given intravenously in a hypertensive woman who had bilateral thoracolumbar sympathectomy in 1948. (A) Effect on supine B.P. (B) Effect on standing B.P. Average supine B.P. prior to study was 243/122 and average standing B.P. 195/118 for 108 determinations over a 55-month period.

Carbethoxysyringoyl methylreserpate was about 20 per cent less potent than reserpine in stimulating hydrochloric acid secretion in the denervated Heidenhain pouch of the dog.

Clinical Material and Method of Study

A total of 30 patients with long-established and relatively stable hypertension were given carbethoxysyringoyl methylreserpate.

Two subjects were given a single intravenous dose and 6 patients a single intramuscular injection of 7.5 mg; all had moderately severe hypertension. Two of these patients subsequently received the drug orally for two weeks in a dosage of 20 mg/day.

Four hospitalized cases with hypertension in the accelerated phase, i.e., grade III or IV fundi of Keith-Wagner, were given 10 to 20 mg/day of carbethoxysyringoyl methylreserpate by the intramuscular route for prolonged periods. This was administered in equal amounts every 12 hours.

Sixteen subjects with mild to moderately severe hypertension received 1 to 20 mg/day by mouth for 6 to 28 weeks. In this group the patients had been observed for at least 4 weeks without therapy followed by 12 weeks on placebo medication. During this period the blood pressure was taken from the left arm with the subject in the supine and standing position. A minimum of 9 determinations was used to derive the average blood pressure. During the interval of carbethoxysyringoyl methylreserpate administration there was a minimum ratio of 9 determinations/16-week period from which the average blood pressures were calculated, except in 1 subject in whom 7 blood pressure determinations in a 6-week period comprised the total from which the average was derived. Included in this group were 10 subjects who had taken oral reserpine for at least 12 consecutive weeks. Their average blood pressure with reserpine was derived from a minimum ratio of 7 blood pressure recordings/12-week period. The blood pressures were usually taken at one or two week intervals.

In two patients, carbethoxysyringoyl methylreserpate was substituted for reserpine as an adjunct to other antihypertensive agents.

Repeated blood counts and urinalyses were done except in those patients who had only acute studies.

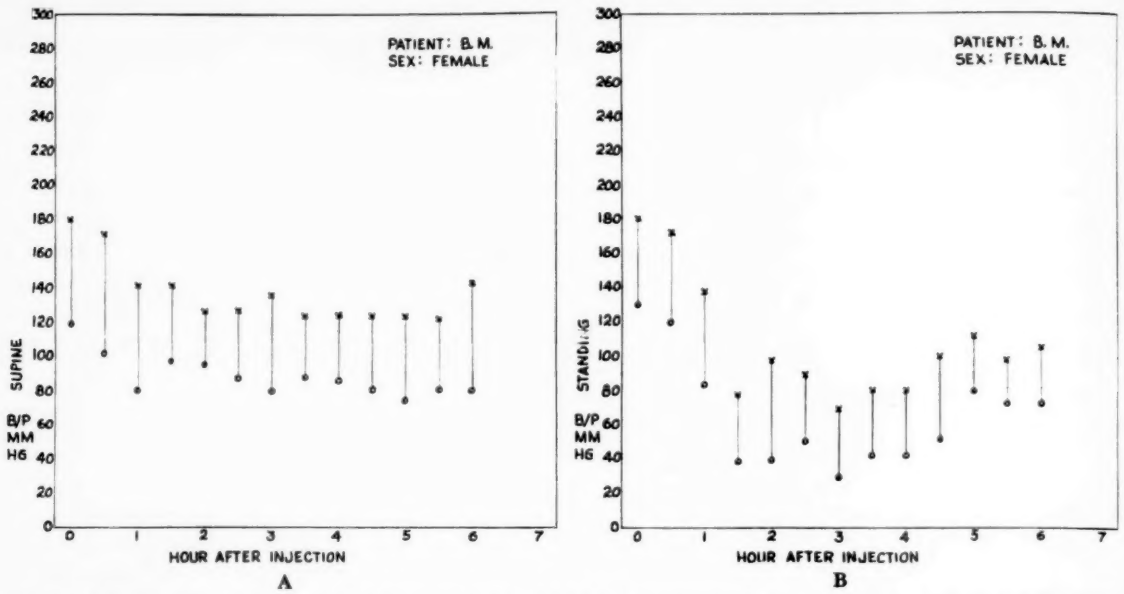

Fig. 3. Effect of 7.5 mg Su-3118 given intravenously. (A) Effect on supine B.P. (B) Effect on standing B.P. Average supine B.P. prior to study was 176/118 and average standing B.P. 181/122 for 32 determinations over a 15-month period.

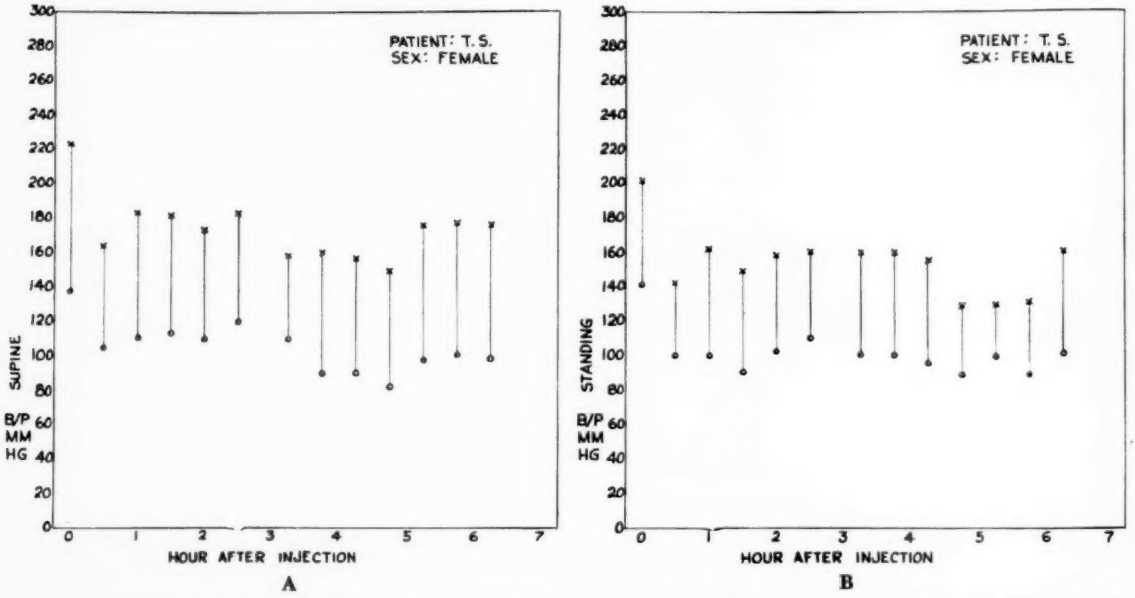

Fig. 4. Effect of 7.5 mg Su-3118 given intramuscularly. (A) Effect on supine B.P. (B) Effect on standing B.P. Average supine B.P. prior to study was 199/116 and average standing B.P. 192/119 for 20 determinations over a 16-month period.

Results

(A) *Single Intravenous or Intramuscular Injections:* The intravenous administration of 7.5 mg of carbethoxysyringoyl methylreserpate caused a marked drop in the blood pressure of each of the two subjects (Fig. 2 and 3). This drop was apparent within one-half hour and at the end of six hours the blood pressure remained markedly lower than prior to the injection. One patient complained of nausea, and moderate tranquilization was apparent in the other. The nausea and tranquilization lasted approximately one

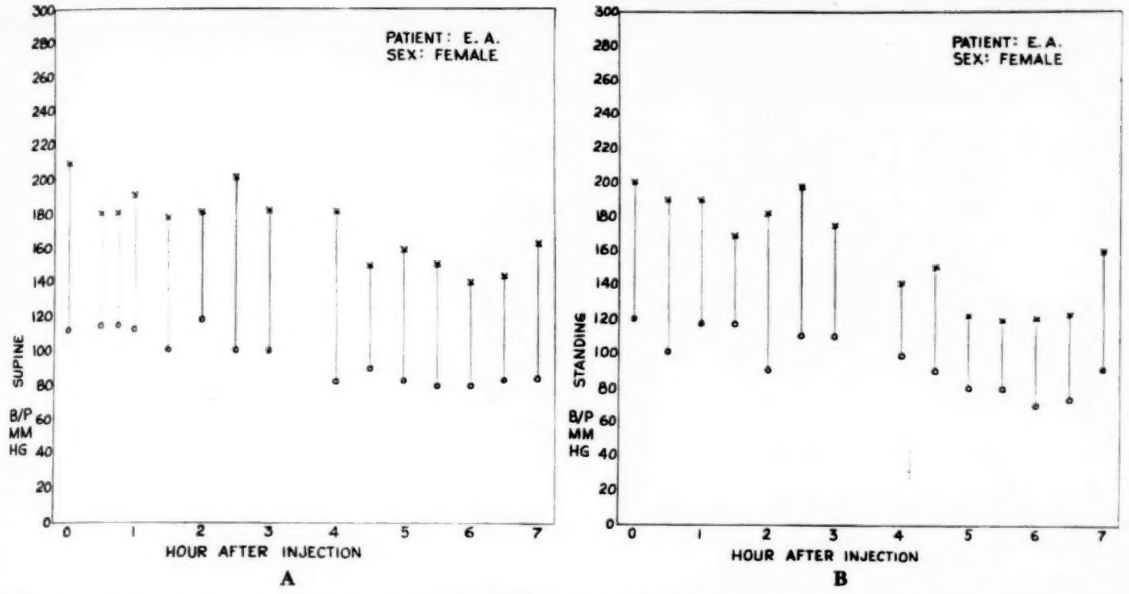

Fig. 5. Effect of 7.5 mg Su-3118 given intramuscularly. (A) Supine B.P. (B) Standing B.P. Average supine B.P. prior to study was 183/100 and average standing B.P. 194/110 for 11 determinations over a 6-month period.

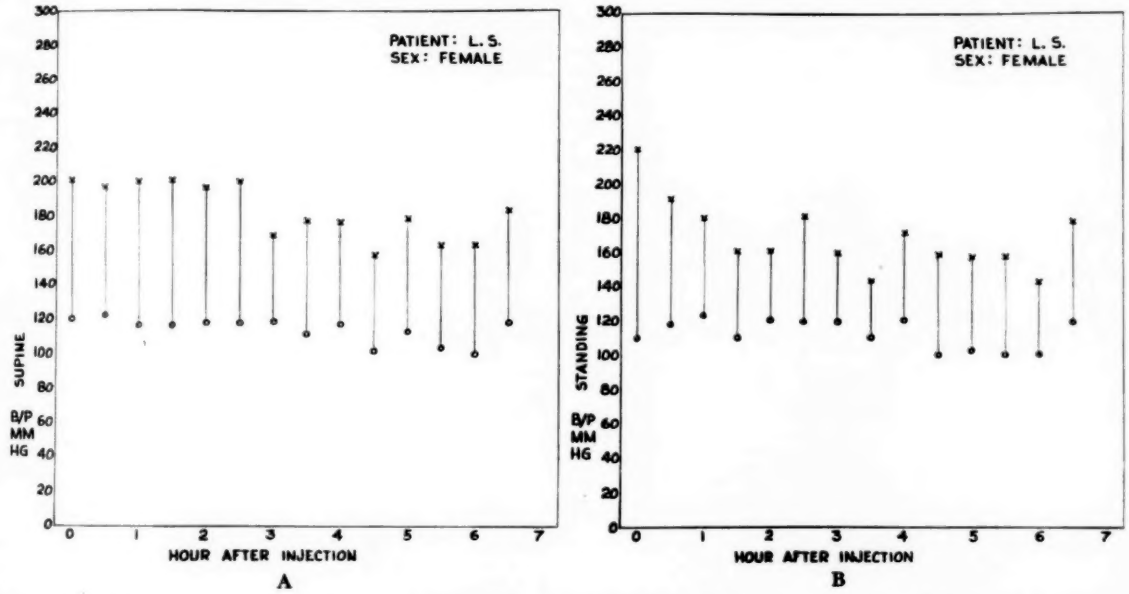

Fig. 6. Effect of 7.5 mg Su-3118 given intramuscularly on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 195/124 and standing B.P. 174/123 for 56 determinations over a 27-month period.

hour. There was slight pain at the injection site. Both cases were later given 20 mg daily by mouth. The decrease in their average blood pressures was slight during the latter regimen.

The 6 patients who received a single intramuscular injection of 7.5 mg of carbethoxysyringoyl methylreserpate did not show uniform responses. In 3 the blood pressure drop was present in both the supine and standing positions (Figs. 4, 5, and 6), while in 2 others a significant drop in blood pressure was observed only in the standing position (Figs. 7 and 8). The re-

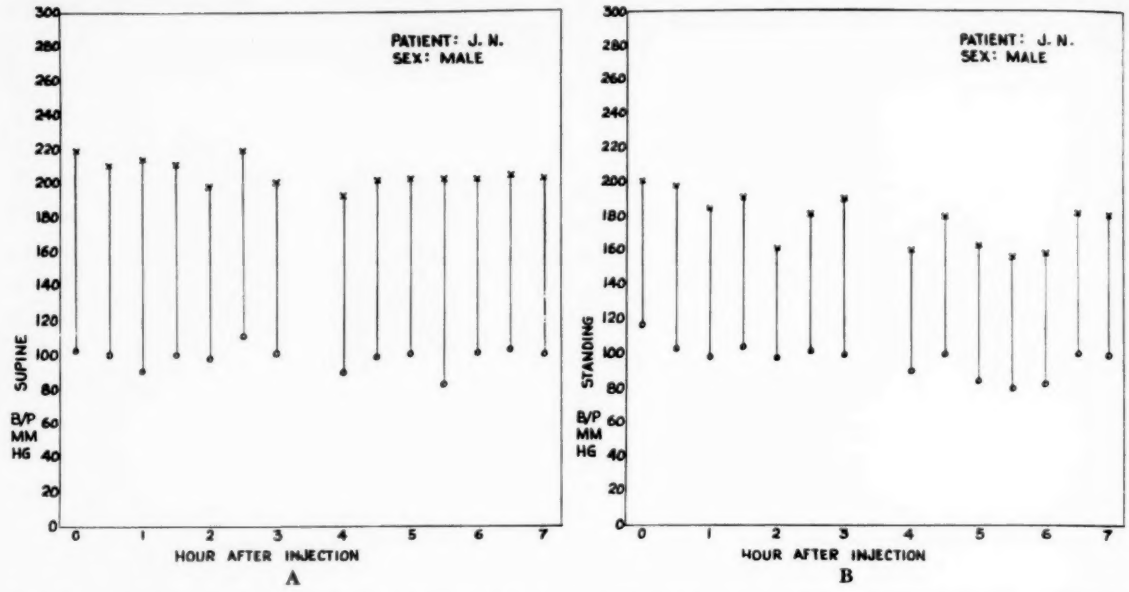

Fig. 7. Effect of 7.5 mg Su-3118 given intramuscularly on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 224/102 and standing B.P. 216/106 for 12 determinations over a 5-month period.

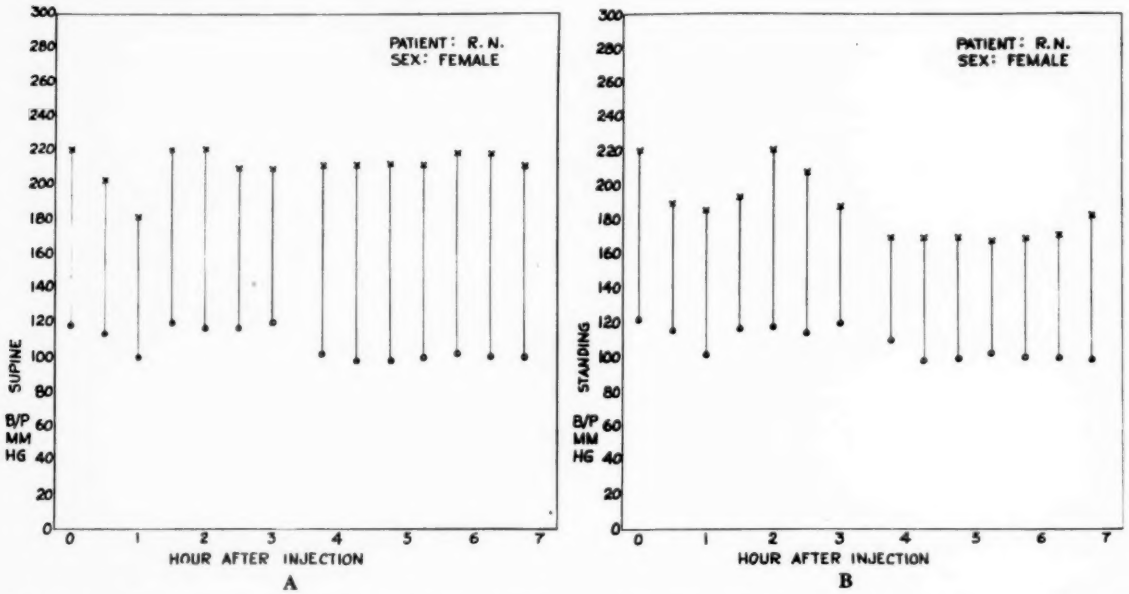

Fig. 8. Effect of 7.5 mg Su-3118 given intramuscularly on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 217/110 and average standing B.P. 200/111 for 30 determinations over a 14-month period.

maining subject exhibited no hypotensive effect (Fig. 9). All 6 patients had some minor local discomfort from the injection, but no other side effects were observed. In all patients who showed a significant fall in blood pressure following intramuscular injection of the drug, the onset was slower than after intravenous administration and the hypotensive effect was still present at the end of six hours.

(B) *Prolonged Intramuscular Administration:* The prolonged administration of carbethoxysyringoyl methylreserpate by the intramuscular

route resulted in a hypotensive effect in the 4 patients studied (Figs. 10, 11, 12, and 13) and was most apparent when the patient was in the standing position. Side effects consisted of slight local pain at the injection site, miosis, and a mild subjective nasal congestion and dryness of the mouth.

TABLE I

Average Supine and Standing Systolic Blood Pressure in 16 Subjects during the Control Period and during the Use of Carbethoxysyringoyl Methylreserpate

Case	Control		Su-3118	
	Supine	Standing	Supine	Standing
1	188	183	162	166
2	211	205	180	180
3	201	208	163	155
4	168	165	152	146
5	196	192	183	174
6	172	175	144	138
7	183	188	152	146
8	164	164	146	135
9	207	212	184	189
10	178	173	170	166
11	236	240	240	232
12	214	217	209	215
13	186	186	193	188
14	248	260	252	256
15	195	190	191	184
16	209	218	202	194

TABLE II

Average Supine and Standing Diastolic Blood Pressure in 16 Subjects during the Control Period and during the Use of Carbethoxysyringoyl Methylreserpate

Case	Control		Su-3118	
	Supine	Standing	Supine	Standing
1	114	119	96	93
2	107	110	89	91
3	122	113	100	103
4	103	108	78	74
5	112	112	94	87
6	122	125	92	93
7	112	117	101	96
8	102	108	88	92
9	115	111	106	92
10	106	109	98	100
11	132	137	128	137
12	127	132	127	129
13	122	117	118	120
14	144	148	150	148
15	110	104	98	100
16	118	108	95	92

(C) *Oral Administration:* Sixteen persons took 1 to 20 mg daily of carbethoxysyringoyl methylreserpate by mouth for periods ranging from 6 to 28 weeks. The average systolic and diastolic blood pressures during the 12-week control period and during the treatment period are shown in Tables I and II. Ten patients in this group had taken reserpine previous to the control period, all with some apparent hypotensive effect. The reserpine had been discontinued in these 10 either because of mental depression or diarrhea. A comparison was made between the average blood pressures while they were taking reserpine and during the administration of carbethoxysyringoyl methylreserpate (Table III). In nearly all cases the decreases in blood pressure were not of major proportions either in response to reserpine or carbethoxysyringoyl methylreserpate, and larger amounts of the latter were required to produce a roughly comparable effect. No recurrence of either mental depression or diarrhea was observed while the patients were taking carbethoxysyringoyl methylreserpate.

(D) Carbethoxysyringoyl methylreserpate

TABLE III

Average Standing Blood Pressure in 10 Subjects While on Reserpine and Carbethoxysyringoyl Methylreserpate. The Average Reserpine Dose Was 0.5 mg/day. The Average Carbethoxysyringoyl Methylreserpate Dose Was 5 mg/day

Case	Reserpine		Su-3118	
	Systolic	Diastolic	Systolic	Diastolic
1	157	90	166	93
2	168	94	180	91
4	150	79	146	74
5	162	86	174	87
6	146	88	138	93
7	137	89	146	96
8	151	95	135	92
9	164	86	189	92
10	150	93	166	100
13	158	100	188	120

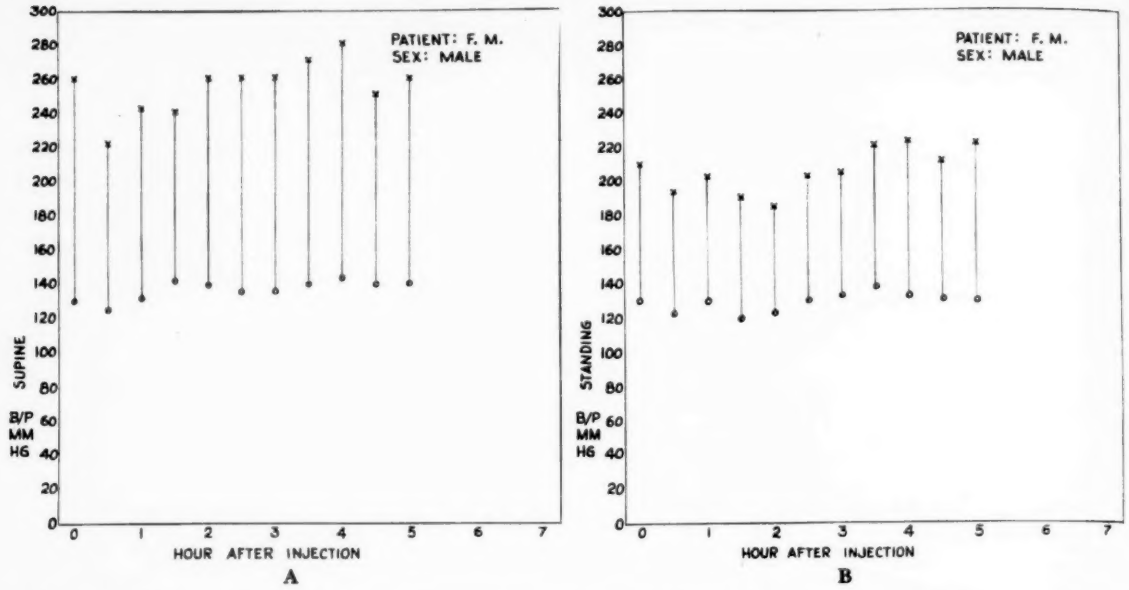

Fig. 9. Effect of 7.5 mg Su-3118 given intramuscularly on supine (A) and standing (B) blood pressures. Average supine B.P. prior to study was 230/140 and average standing B.P. 180/116 for 16 determinations over a 6-month period.

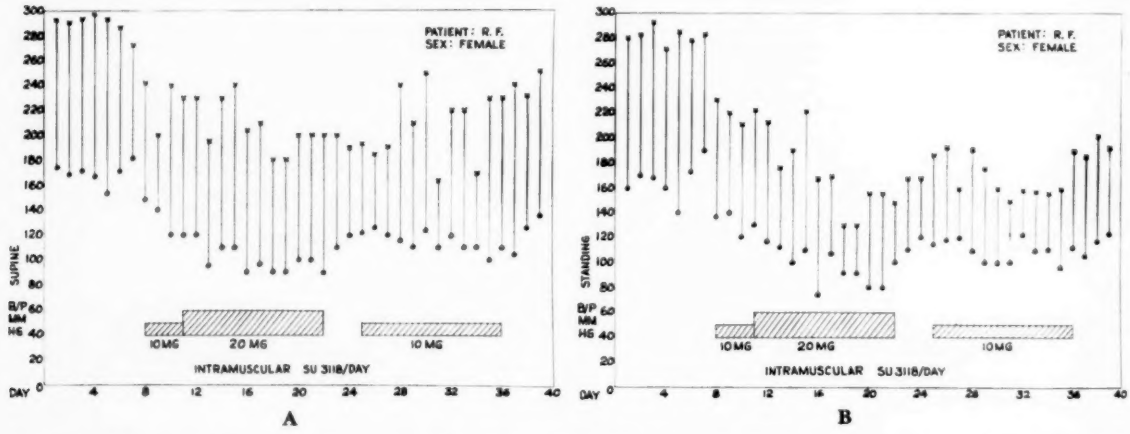

Fig. 10. Effect of prolonged intramuscular administration of 10–20 mg Su-3118 daily on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 282/166 and standing B.P. 284/166 for 7 determinations over a one-week period.

was substituted for reserpine in 2 patients as an adjunct to other hypotensive agents. The results are depicted in Figures 14 and 15.

(E) The blood counts and urinalyses remained normal in every instance.

Discussion

When administered by the intravenous or intramuscular routes, carbethoxysyringoyl methylreserpate has a greater hypotensive effect than equivalent amounts given by mouth. This would indicate either incomplete absorption or partial inactivation during or after absorption from the gastrointestinal tract.

Larger amounts of intramuscular and oral carbethoxysyringoyl methylreserpate are required to produce hypotensive effects of a degree comparable to those following reserpine. However, no lethargy or tranquilization occurred after rather prolonged intramuscular

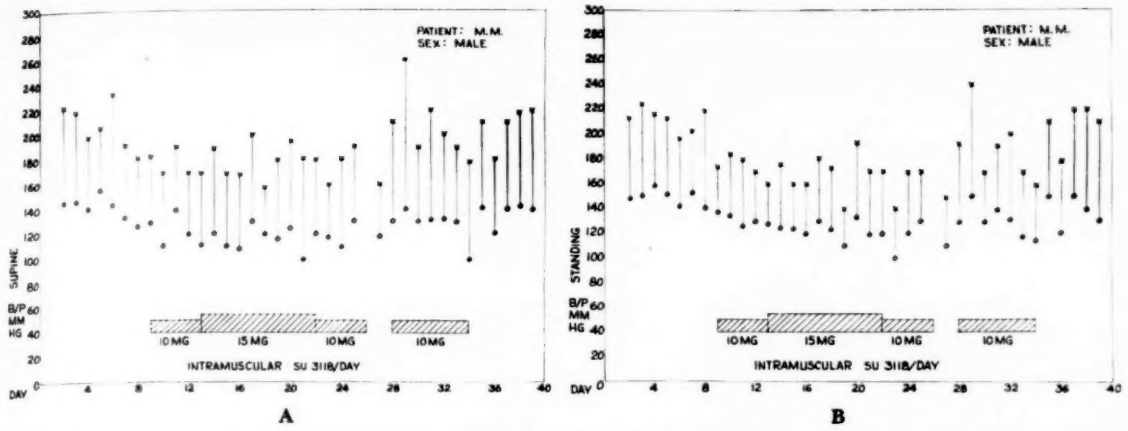

Fig. 11. Effect of prolonged intramuscular administration of 10–15 mg Su-3118 daily on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 207/142 and average standing B.P. 212/149 for 7 determinations over a one-week period.

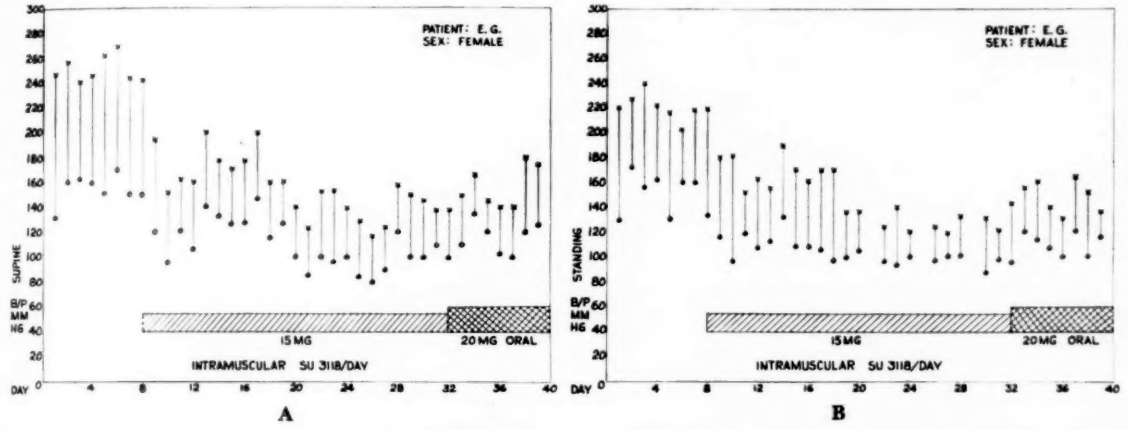

Fig. 12. Effect of prolonged intramuscular administration of 10–20 mg Su-3118 daily on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 239/154 and average standing B.P. 222/150 for 7 determinations over a one-week period.

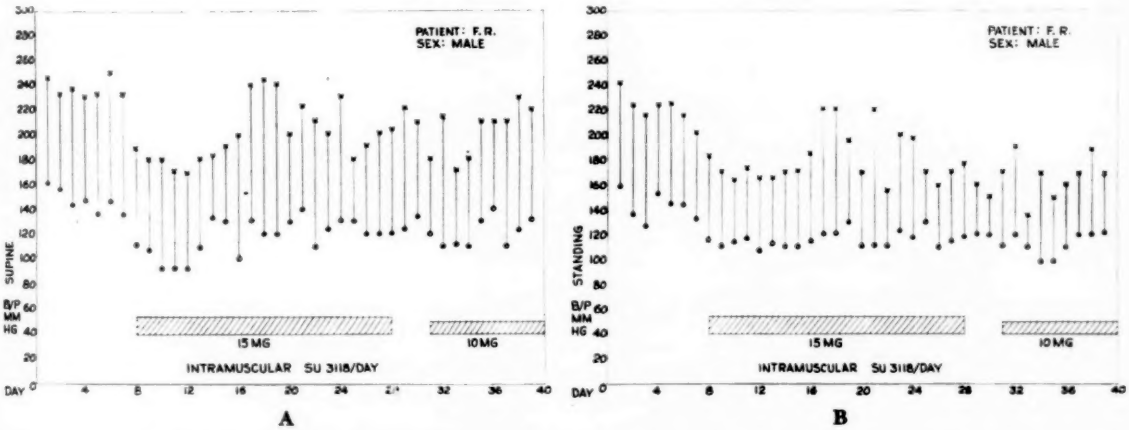

Fig. 13. Effect of prolonged intramuscular administration of 10–15 mg Su-3118 daily on supine (A) and standing (B) blood pressure. Average supine B.P. prior to study was 236/147 and average standing B.P. 221/143 for 7 determinations over a one-week period.

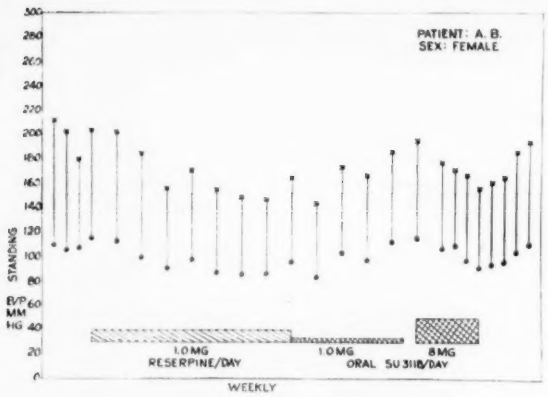

Fig. 14. Effect of substituting oral Su-3118 for reserpine on standing blood pressure. The patient also was receiving 50 mg of hydralazine daily.

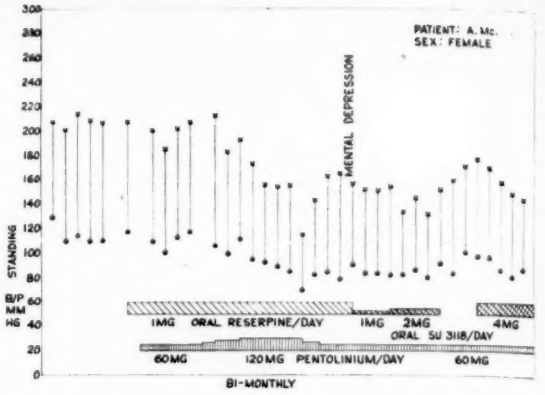

Fig. 15. Effect on standing blood pressure of substituting oral Su-3118 for reserpine as an adjunct to pentolinium therapy.

use of the former, while these side effects invariably appear when intramuscular reserpine is given over a similar length of time in a dosage sufficient to produce at least a comparable hypotensive effect.

The patients treated with intramuscular carbethoxysyringoyl methylreserpate had severe hypertensive disease and their responses to this drug were encouraging. Any preparation that helps control this phase of hypertension for an extended time without serious side effects is of value.

Oral carbethoxysyringoyl methylreserpate caused only minor side effects and in no instance had to be discontinued because of these. As with reserpine, it is probable that the efficiency of the oral drug is limited in hypertensive patients when it is the sole agent used. The lack of side effects of carbethoxysyringoyl methylreserpate in patients unable to tolerate reserpine should prove of value in the treatment of hypertension.

Summary

(1) Single intravenous doses of carbethoxysyringoyl methylreserpate given to 2 patients with moderately severe hypertension produced a marked hypotensive effect.

(2) Four individuals with severe hypertension in the accelerated phase showed encouraging responses to prolonged intramuscular administration of this new drug.

(3) In the oral form, carbethoxysyringoyl methylreserpate can be given in relatively large doses without serious side effects. This should be of value in those patients unable to tolerate reserpine.

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Meprobamate in Treatment of Hypertension

Its Effects Alone and in Combination with Mecamylamine*

LINN J. BOYD, M.D., F.A.C.C., VICTOR F. HUPPERT, M.D., MICHAEL G. MULINOS, M.D., PH.D., *and* HARVEY HAMMER, A.B.

New York, New York

NEUROGENIC impulses play an important role in the aggravation of hypertension, especially in hyperkinetic subjects. The influence of psychogenic impulses can be eliminated, and thus determined for any one subject, through the use of the so-called Amytal test; the influence of reflex neurogenic impulses can be blocked out by agents such as mecamylamine acting on the autonomic ganglia, or through paralysis of the sympathetic receptors, and by spinal anesthesia.

Because many of the symptoms of uncomplicated hypertension respond to the combination of reassurance, mental rest, sedatives, and time, it was to be anticipated that the central depressants classed as "tranquilizers" should have similar effects in the reduction of the hypertension and in lessening the rise in blood pressure resulting from emotional upsets.[1]

PROCEDURE

The effects of meprobamate† on the blood pressure were determined in three separate studies, each having its special purpose.

In the first study, 12 subjects were observed in the outpatient clinic of Flower and Fifth Avenue Hospital. These subjects were started on meprobamate, 0.4 Gm, four times a day. In 7 subjects, mecamylamine was added following one to twenty weeks of meprobamate administration. The initial dose was 2.5 mg, usually given twice a day, with the meprobamate.

The second study consisted of 18 subjects with moderate to severe hypertension. Thirteen were given the Amytal test in order to determine the part played by neurogenic impulses in the severity of the hypertension. All subjects received meprobamate, 0.4 Gm, three times a day, orally. As soon as it was determined that the meprobamate effect had plateaued, 4 subjects received mecamylamine, 2.5 mg, three times a day, in addition to the meprobamate. One patient received mecamylamine initially, followed by meprobamate.

The third, and largest, part of this study was made in the wards of the Bird S. Coler Hospital for chronic diseases. Fifty-seven subjects received only meprobamate, 0.4 Gm, three times a day, orally. The plan included a twofold control to guard against seasonal and other unpredictable fluctuations in blood pressure. One control consisted of a group of 29 subjects who received only placebo capsules throughout the period of observation; the other control consisted of a period of several weeks during which placebo capsules were substituted for the meprobamate, without the knowledge of the patients or the examining physicians.

This study, as a whole, included frequent, periodic determinations of the blood pressure in a total of about 116 subjects. The observations included urine studies, hemograms, electrocardiogram when indicated, and records of appetite, body weight, and untoward reactions.

* From the Departments of Medicine, and Physiology and Pharmacology of the New York Medical College, Metropolitan Medical Center, New York, New York.

† Meprobamate (Miltown) tablets and capsules were generously supplied by Dr. Frank M. Berger of Wallace Laboratories, New Brunswick, New Jersey.

TABLE I
Meprobamate Blood Pressure Study
Data by hospitals

Hospital and status	No. cases	Sex F	Sex M	Age (average)	Medication: Meprobamate	Medication: Mecamylamine	Medication: None
Flower-Fifth OPD	12	8	4	61 (40–78)	12	8	0
Flower-Fifth hospitalized	18	14	4	60 (37–82)	18	4	0
Coler hospitalized	86	42	44	72 (48–95)	57	0	29
TOTALS	116	64	52		87	12	29

A summary of the case material will be found in Table I.

RESULTS

Detailed analysis of the results obtained from the three parts of this study revealed a moderate but definite and statistically valid fall in blood pressure in response to the meprobamate medication. The group of 12 subjects receiving mecamylamine in addition to the meprobamate is too small to allow a definite conclusion on the effects of mecamylamine on the blood pressure. Mecamylamine was discontinued following publication of data suggesting toxicity from clinical doses.[2]

FLOWER-FIFTH AVENUE OUTPATIENT GROUP

Twelve subjects were included in this study (see Table I). Prior to receiving any medication, the blood pressures averaged 178/95 mm Hg, with a range of 150–220 mm systolic and 70–112 mm diastolic (see Table II). Initially, all received tablets of meprobamate 0.4 Gm four times a day. Upon the appearance of symptoms of overdosage, the dose was reduced to three tablets a day in 4 subjects, and to two tablets a day in 1 subject. Four received the medication daily for from two to three months, and 8 for from four to six months. Obviously, in a study of this kind, each patient had to be depended on to take the drug as prescribed. For this reason, these data are less reliable than those obtained on hospitalized subjects. The blood pressure changes are summarized in Table II.

Eight of the 12 subjects complained of dizziness, or of feeling overtired, especially during the first weeks of therapy. In 4 of these 8, the dose was reduced to three tablets per day. In only one case was it necessary to reduce the dose of meprobamate to two tablets per day. There were no symptoms other than those ascribed to overdosage. No evidence of habituation occurred, and there were no symptoms referable to the withdrawal of the meprobamate.[3]

FLOWER-FIFTH AVENUE HOSPITALIZED GROUP

Eighteen subjects with moderate to severe, chronic hypertension were treated with meprobamate alone or combined with mecamylamine. The meprobamate was given orally in a dose of 0.4 Gm three times a day initially in all but one subject (see Tables I and II).

Meprobamate Alone: The data summarized in

TABLE II
Meprobamate Blood Pressure Study
Flower-Fifth Avenue Hospital, OPD group

Medication	No. cases	Blood pressure (mm Hg): Initial S	Initial D	Final[a] S	Final[a] D	Diff. S	Diff. D	No. showing change: Over	None	Less
Meprobamate alone	5	176	88	155	89	−21	+1	0	1	4
Meprobamate and mecamylamine	7	181	101	171	94	−10	−7	2	0	5
TOTALS	12	178	95	153	85	−25	−10	2	1	9

[a] After 3 to 6 months of daily medication.

TABLE III

Meprobamate Blood Pressure Study
Flower-Fifth Avenue Hospital, hospitalized group

Procedure	No. cases	Blood pressure (mm Hg)								
		Initial		Final[a]		Diff.		No. showing change		
		S	D	S	D	S	D	Over	None	Less
Amytal test (pretreatment)[b]	13	222	120	183	108	−39	−12	0	0	13
Meprobamate therapy[b]	13	222	120	180	96	−42	−24	0	0	13
Meprobamate (All cases)[c]	18	215	117	167	101	−48	−16	0	0	18

[a] After 3 to 19 days of treatment.

[b] These 13 subjects are listed in this way for comparison of effects on blood pressure between Amytal test (gr. 3) and treatment with meprobamate for from 3 to 19 days.

[c] Includes 5 subjects who received mecamylamine.

Table III indicate conclusively that meprobamate 0.4 Gm three times a day will reduce the blood pressure to the level indicated as basal by the Amytal test. This result is highly significant statistically, not only because of the average fall in blood pressure of 48 mm Hg, but also because the blood pressure was reduced in every case.

The effects of meprobamate in lowering blood pressure are rapid, being evident during the first day in most cases. The average blood pressure after 48 hours of meprobamate administration was 179/107, compared to an initial pressure of 215/117 mm Hg.

No untoward reactions were reported by these subjects. The short duration of treatment in some cases was due to discharge from the hospital. Perhaps the blood pressure in some of these subjects would have been decreased further with more prolonged treatment.

Meprobamate Combined with Mecamylamine: It is difficult to draw any definite conclusions from the four patients who received mecamylamine in conjunction with the meprobamate. The average blood pressure initially in these four cases was 234/119 mm Hg compared to 142/93 mm Hg at the end of treatment, and represents an average fall of 92 mm Hg systolic and 24 mm Hg diastolic. The combination of meprobamate with mecamylamine may have been more effective than either drug used alone, but further analysis of the data renders this unlikely. The four subjects on the meprobamate-mecamylamine combination had been treated for longer periods, with an average of 12 days (6 to 16), compared to an average of 7.8 days for all 18 subjects, and to 6.8 days for the 14 subjects receiving meprobamate alone. In one case mecamylamine alone for 7 days reduced the blood pressure, but addition of meprobamate reduced it still further.

THE COLER HOSPITAL STUDY

The subjects studied at this institution were elderly and for the most part under custodial care. The group consisted of 57 hypertensive and normotensive subjects who received meprobamate, and 29 men and women who received only placebo medication. Because the blood pressure of elderly people varies widely, is in-

TABLE IV

Meprobamate Blood Pressure Study
Coler Hospital group, background data

Medication	Sex	No.	Age (average)	Body weight (lb)	
				Initial	Final[a]
Placebo	F	14	63 (48–92)	132 (101–207)	133 (99–207)
Placebo	M	15	74 (56–86)	145 (92–186)	143 (91–186)
Meprobamate	F	28	76 (56–95)	137 (91–293)	135 (90–285)
Meprobamate	M	29	74 (51–88)	152 (92–204)	148 (89–199)

[a] After 6 to 8 weeks of observation.

TABLE V

Meprobamate Blood Pressure Study

Coler Hospital group, summary of blood pressure data

Medication	Sex	No.	Average blood pressure (mm Hg)				
			Initial	6–8 weeks of therapy	Post-study 6 weeks[a]	Post-study 15 weeks	Post-study No.[b]
Placebo	F	14	146/88	136/75	—	149/88	10
Placebo	M	15	148/84	141/79	—	152/87	12
Totals		29	147/86	139/77	—	151/87	22
Meprobamate	F	28	154/86	142/86	146/76	160/90	26
Meprobamate	M	29	141/83	127/75	134/77	140/83	22
Totals		57	147/85	135/80	140/77	154/87	48

[a] The meprobamate group received the placebo during this period.

[b] This is the number available for checkup at 15 weeks.

fluenced by weather, and is affected by emotional disturbances, it was deemed important to insure that any changes in blood pressure that occurred during meprobamate medication were not coincidental to extraneous events. As further insurance against such a contingency, a second control was instituted, in that eventually the meprobamate was substituted by a placebo dosage form without the knowledge of the patients.

Table IV gives the pertinent clinical data at the beginning of the study and includes the body weight at the end as well. There was no change in body weight during the period of medication.

The blood pressures were determined at regular intervals in all members of the four groups shown in Table V. During the administration of either the placebo or the meprobamate, the subjects were questioned about appetite, sleep habits, diurnal somnolence, changes in physical activities, or other evidence of drug action. All untoward symptoms were recorded, regardless of any suspected association with the medication.

The medication consisted of capsules, given three times a day. The medicated capsules contained 0.4 Gm of meprobamate; the placebo capsules were of the same size and color as the medicated ones. The meprobamate medication was given daily for about eight weeks, at which time it was substituted with the placebo capsule for five weeks.

TABLE VI

Meprobamate Blood Pressure Study

Coler Hospital group, summary of changes in blood pressure, all groups

Medication	Sex	No.	Difference in B. P.[a]				Direction of B. P. change: None[c]	Rise	Fall	
			mm Hg	σ	r	t[b]	No.	No.	No.	%
Placebo	F	14	−10	18.6	4.84	2.05	3	3	8	57
Placebo	M	15	−7	18.0	4.65	1.50	6	3	6	40
Totals		29	−8.5	18.3	3.40	2.50	9	6	14	48
Meprobamate	F	28	−12	24.8	4.67	2.56	7	5	16	57
Meprobamate	M	29	−14	26.2	4.84	2.90	4	8	17	58
Totals		57	−13	25.5	3.38	3.83	11	13	33	58

[a] Difference between initial systolic B. P. and B. P. after 6 to 8 weeks of observation.

[b] A t value of 2.5 or over is statistically significant.

[c] No change in B. P. if less than 10 mm Hg in either direction.

TABLE VII

Meprobamate Blood Pressure Study
Coler Hospital group, summary of changes in blood pressure in cases with initial systolic B. P. of 140 mm Hg or over

Medication	Sex	No.	Difference in B. P.[a]				Direction of B. P. change			
							None[b]	Rise	Fall	
			mm Hg	σ	r	t	No.	No.	No.	%
Placebo	F	9	−11	19.0	6.30	1.72	2	2	5	55
Placebo	M	9	−14	19.0	6.30	2.22	3	2	4	45
Totals		18	−13	19.0	4.48	2.75[c]	5	4	9	50
Meprobamate	F	19	−22	15.0	3.20	6.86[c]	4	0	15	79
Meprobamate	M	12	−28.5	31.8	9.20	3.10[c]	1	2	9	75
Totals		31	−24.5	23.2	4.16	5.88[c]	5	2	24	77
P. vs. M.			−11.5	30.0	6.05	1.95[d]				

[a] Difference between initial systolic B. P. and B. P. after 6 to 8 weeks of observation.
[b] No change in B. P. if less then 10 mm Hg in either direction.
[c] These values indicate a statistically significant difference between the initial and final blood pressure.
[d] Statistically significant due to the larger number of cases (49) involved.

Comparison of Meprobamate and Placebo Effect on B. P.: Table V also summarizes the data on blood pressure in each of the four groups of subjects; i.e., meprobamate, male and female subjects, and placebo, male and female subjects. There was a slight fall in blood pressure in all four groups. The fall was somewhat more marked in the meprobamate recipients, with a tendency toward a rise to the previous level when the placebo was substituted for the meprobamate. For example, as shown in Table VI, the average drop in blood pressure in the placebo control group was 8.5 mm Hg, with 14 of the 29 subjects (48 per cent) participating in the fall. The average drop in blood pressure in the meprobamate group was 13 mm Hg, 33 of the 57 subjects (58 per cent) participating. Statistical analysis of the data in both groups shows that the fall in the blood pressures during the period of observation was not accidental. However, the fall in blood pressure in the placebo group was smaller than in the meprobamate group, but the difference was not statistically significant.

Meprobamate and Placebo Effects in Mildly Hypertensive Subjects: Each of the two groups of subjects contained a number of normotensive individuals (blood pressure under 140 mm Hg systolic), whose blood pressures would not be expected to fall with sedative medication (negative Amytal test). Table VII gives data on the effect of medication on the blood pressures of those subjects with initial pressures of 140 mm Hg or over.

The data show that the average fall in blood pressure in 18 such subjects receiving the placebo was 13 mm Hg and occurred in 9 (or 50 per cent). They show also that the average fall in 31 "hypertensive" subjects receiving the meprobamate was 24.5 Hg and occurred in 24 (77 per cent) of subjects. The drop in blood pressure that occurred in both groups was calculated to be statistically significant; i.e., the summer heat (May 30 to August 14) apparently induced a fall regardless of medication. This fact justifies the extra work of including the placebo group; otherwise the influence of the meprobamate would have been somewhat misleading.

Table VII further shows the difference in blood pressure fall between the placebo group (13 mm Hg) and the meprobamate group (24.5 mm Hg) was statistically significant, and that the meprobamate administration did indeed lower the blood pressures of 77 per cent of these mildly hypertensive subjects.

Side Effects: Table VIII shows the various complaints registered during the administration of the meprobamate and placebo medications to the Coler group of subjects. The symptoms were listed without attempt at interpretation of the cause. It was felt that the double-blind technic used and the double-control approach would cancel those reactions

TABLE VIII
Meprobamate Blood Pressure Study
Coler Hospital group, summary of complaints and reactions[a]

Medication	Sex	No.	Type of complaint and incidence[b]						
			GI	Rash	CNS	Falls[c]	Other	Total No.	Total %
Placebo	F	14	1	0	4	1	5	10	66
Placebo	M	15	4	4	1	0	1	9	60
Meprobamate	F	28	8	1	7	5	6	17	61
Meprobamate	M	29	3	3	6	6	7	15	52
Totals		86	16	8	18	12	19	51	59

[a] Does not include change in diurnal dozing or drowsiness.

[b] Some patients had symptoms in more than one category.

[c] Three of the meprobamate patients stumbled and fell before treatment.

which had no connection with the meprobamate medication.

It is evident from the summary data in Table VIII that the rate of occurrence of complaints was about the same in all groups, regardless of medication. Obviously, in the determination of side effects those due to the pharmacologic effects of meprobamate as a central depressant must be considered separately. Gastrointestinal upsets were about the same in the medicated and placebo groups. Rashes appeared in four patients in the meprobamate group and four in the placebo group. All rashes disappeared in time, without the discontinuance of treatment.

Neurologic symptoms (see Table VIII) included dizziness, headache, mental confusion, nervousness, etc. Increased diurnal sleeping is not included. The number of stumbling falls was greater in the meprobamate than in the placebo group, and can be ascribed to the pharmacologic effects of the meprobamate. Therefore, they must be regarded as indicative that the daily dose of 1.2 Gm was having its full effects. A reduction in the dose would be indicated in these subjects. However, analysis of nurses' and staff notes indicated that only five of the nine patients who fell while receiving meprobamate did so because of the CNS effects of the drug. There were no withdrawal symptoms upon substitution of a placebo capsule for the one containing the meprobamate.[3]

Discussion

For the purpose of this study, hypertension has been considered as a sustained elevation of the systolic blood pressure at a level of above 140/90 mm Hg[4] as ascertained by the usual brachial manometric methods. The patients studied herein were, for the most part, elderly, and the elevation in blood pressure was of a chronic nature.

The pathologic physiology of hypertension includes genetic, humoral, geriatric, and pathologic mechanisms as etiologic factors in the appearance and progression of a rising arterial pressure. Whatever the origin, it would seem that the activity of the nervous system, in most if not all instances, in contributing to the degree of vasoconstriction results in acute exacerbations of hypertension and may even initiate the state. The actual degree of effect elicited by mental disturbances is dependent wholly upon the ability of the arterioles to contract, and upon the efficiency of the compensating reflex and humoral mechanisms which are activated by an acute rise in arterial pressure. For example, the more chronic the hypertension and the greater the arteriosclerotic process, the less will be the influence of nervous impulses in further raising the pressure and of Amytal in lowering it.

The role played by nervous centers at and above the medulla in the etiology of hypertension can be surmised through the use of diagnostic and therapeutic procedures which lessen or eliminate the activity of such centers. Sympathectomy, sympatholytic and autonomic gangliolytic agents, and selective central depressants have been employed, more or less successfully, in controlling the more severe exacerbations of hypertension. The majority of patients who die of hypertensive disease die as the result of heart failure or cerebral hemorrhage.[5] It is therefore helpful to reduce to a minimum the frequency and extent of the exacerbations of pressure, usually due to nervous stimuli, thus lessening the work load upon the heart and tension upon the arterioles.

The selection of any combination of therapeutic agents for the treatment of the neurogenic or psychosomatic influences on the hypertensive process is a rather simple pharmacodynamic problem. Clinically, however, the day-to-day care of these patients is predicated on a painstaking individualization of the doses of each preparation so as to avoid annoying side effects which are often more disturbing to the patient than the relatively asymptomatic hypertension. For this reason, the most effective remedy for the greatest number will be one that requires no narrowly critical dose for the avoidance of side effects. Prolonged administration should result in little or no cumulation, habituation, or dependence. It should elicit a minimum of side effects, such as dizziness, somnolence, dry mouth, constipation, dysuria, difficulties in focusing, or sudden bouts of hypotension leading to fainting spells, so commonly seen with the sympatholytic and ganglioplegic drugs.

Central nervous system depressants, especially the barbiturates, have proved effective in reducing psychogenic hypertension. Likewise, many ganglionic agents have been used, but the side effects are often severe, the dosage is individually critical, and the effects of overdosage lead to disturbing symptoms of autonomic depression and shock.

Nussbaum *et al.*[6] used a combination of mecamylamine, a ganglionic depressant, and meprobamate, a tranquilizer, in the treatment of 37 patients with moderate to severe hypertension, on an outpatient basis. Mecamylamine was found to control successfully the blood pressure in 28 of 37 subjects. While meprobamate alone had no effect, given with mecamylamine it provided objective and subjective improvement in 35 of the 37 patients.

Summary and Conclusions

(1) A study has been conducted to determine the effects of meprobamate in mild vascular hypertension. It was expected that this central relaxer would be of benefit in the tense, worrisome, and hyperkinetic patient.

(2) The study included two small series of hypertensive subjects, one made up of outpatients, the other of bedridden patients with more severe hypertension. A third, and larger, series consisted of both normotensive and hypertensive custodial-care patients, under strictly controlled regimens of meprobamate and/or placebo therapy.

(3) The custodial-care patients were divided into those with hypertension and those with resting systolic blood pressures below 140 mm Hg. Both the meprobamate- and placebo-treated groups received the medication daily during a six- to eight-week period of observation.

(a) The 31 patients with hypertension in the latter group responded to meprobamate medication with a fall in pressure which was statistically greater than in the 18 subjects with hypertension who had been treated only with the placebo.

(b) Upon discontinuance of the meprobamate therapy, there was a slow rise in blood pressure toward the pretreatment level. This was considered as further evidence that the meprobamate had been responsible for the greater reduction in blood pressure seen in these patients, compared to the reduction in the control group.

(c) Except for an increased degree of somnolence and a greater incidence of stumbling falls, side effects were no more frequent with the meprobamate regimen than in the patients receiving the placebo.

(4) It is concluded that a daily dose of two or three 0.4 Gm meprobamate tablets is a useful adjunct in the treatment of the psychogenic and neurogenic components of hypertension.

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Depts of Med. Phys. + Pharmacology, New York Med College

Seminar on Ballistocardiography*

Practical Value of the Ballistocardiogram in Myocardial Infarction†

JEAN DESRUELLES, M.D., JEAN-F. MERLEN, M.D., *and* G. DEBACKER, M.D.

Lille, France

THE BALLISTOCARDIOGRAM is the mirror of the mechanical activities of the myocardium and, as such, one must expect severe abnormalities in its morphology during myocardial infarction.

Prinzmetal and his co-workers[1] have shown, through ultrarapid cinematographic experiments in operating upon a dog, that 5 seconds after the tying of a coronary artery the ischemic portion of the myocardium no longer contracts. After some seconds this ischemic portion presents a systolic dilatation.[2]

Clinically, following myocardial infarction, the heart presents zones of less apparent contractility which later bulge during systole, findings similar to those in the experiments on dogs. These areas of diminished contractility unquestionably modify the pattern of applied heart force which originates the ballistocardiographic curves. De Soldati[3] gives this as an explanation of the abnormality of the ballistocardiogram during coronary diseases in general and in myocardial infarction in particular. Whatever the cause may be, the ballistocardio gram is always susceptible to the influence of coronary occlusion.

We present here our studies of the ballistocardiographic curves found during myocardial infarction, and demonstrate the practical importance of ballistocardiography in the establishment of its diagnosis and prognosis. All of our curves are recorded according to the electromagnetic method of Dock and Taubman.[4] When atypical curves appeared, we classified them according to the Brown[5] classification.

THE BALLISTOCARDIOGRAM DURING THE ACUTE PHASE CF MYOCARDIAL INFARCTION

During the acute phase of infarction, the course of which is conventionally accepted to last two months, the ballistocardiographic patterns are very often distorted. The anomalies resemble those seen during angina pectoris; the curve usually shows generalized diminution of all the waves (hypokinesis) (Fig. 1). On the other hand, there sometimes exists so severe an abnormality that it appears difficult to distinguish the individual waves (Fig. 2). These abnormalities are not influenced by the type or location of the infarction nor by its severity and extent.

The diagnosis of myocardial infarction is based primarily on the clinical signs: precordial pain, lasting for hours despite the nitrate derivatives, and sometimes followed by collapse and by a more or less significant hypotension and fever. In most cases the electrocardiogram is of the greatest importance at the time of the acute phase and confirms the diagnosis. Rarely (three times out of a hundred cases), the electrocardiogram may be normal when the clinical appearance is characteristic. When this oc-

* This issue contains Part V of the Seminar on Ballistocardiography. A schedule of the articles already published, and of future articles in this seminar, may be found on pp. 101-102 of the January, 1959, issue (Vol. III, No. 1).

† From the College of Medicine and the Hospital, Lille, France.

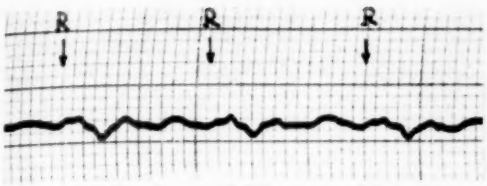

Fig. 1. A female, aged 73 years, with postero-lateral myocardial infarction. BCG during sixth week shows low voltage ("hypokinetic").

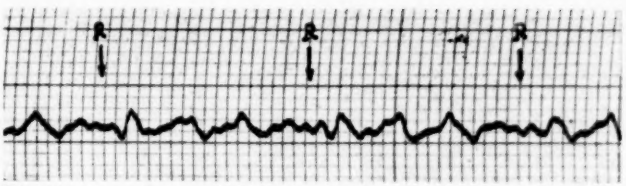

Fig. 2. A male, aged 43 years, with anterolateral myocardial infarction. BCG on the fifteenth day is graded type IV, showing significant abnormalities with low voltage.

curs the ballistocardiogram is always truly pathologic, Brown type III (Fig. 3) or IV, and confirms the diagnosis of coronary disease.

One may attribute these differences to the rapidity of evolution of the metabolic disturbance caused by the acute coronary insufficiency or to the area of the myocardial lesion being too small to modify the electrocardiographic curve. Further, we had two patients with typical angina and a third with atypical symptoms in whom we were able to recognize the imminence of myocardial infarction because of b listic curves of type III and IV despite a normal electrocardiogram. In these three cases the infarction happened two or three weeks later. However, in most cases a ballistocardiogram is only to be considered as a help in the diagnosis of acute coronary occlusion. Clinical diagnosis and electrocardiography are first in importance, the ballistocardiogram being of documentary importance only.

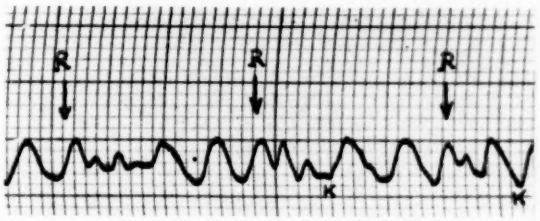

Fig. 3. Male, aged 46 years, with postero-inferior myocardial infarction. BCG during sixth week shows early M configuration (HI waves); "crushed" J wave, "crooked" JK wave, type III abnormality.

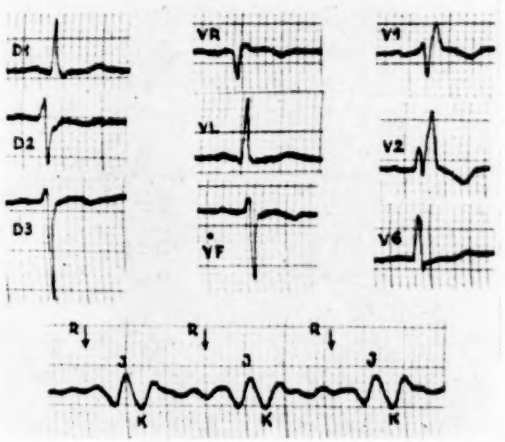

Fig. 4. Male, aged 60 years, with history of first myocardial infarction in 1949 (inferior and posterolateral) and second infarction in November, 1955. ECG in May, 1957, shows right bundle branch block, but BCG is normal.

The Ballistocardiogram After the Acute Phase of Myocardial Infarction

We have reported in detail about 100 cases of infarction followed by serial electrocardiograms and ballistocardiograms for periods ranging from several months to 15 years. After the acute phase, i.e., beyond the end of the second month, careful study of the serial ballistocardiographic tracings of each patient will reveal either a progressive return toward normal or the persistence of the ballistocardiographic anomalies which appeared during the acute phase.

Seldom does the ballistocardiogram revert to absolutely normal after an infarct,[8,9] for the coronary disease continues its course after organization of the infarction. One must not forget that coronary sclerosis alters the form of the ballistocardiogram. On only two occasions did the ballistic curves appear normal while the electrocardiogram was still abnormal. In one of these, an anterior infarction in a man 54 years of age was clinically healed within one month, yet after a two-year interval the electrocardiogram was still abnormal although the ballistocardiogram was quite normal. The other patient, a 60-year-old male, suffered two infarctions, the second one six years later. The ballistocardiogram was quite normal seven years after the first infarction but electrocardiograms were still abnormal (Fig. 4).

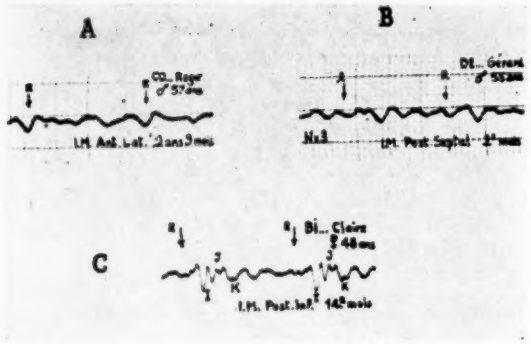

Fig. 5. Very abnormal BCG tracings following myocardial infarction correlating well with severe symptoms. (A) Male, 57 years of age with heart failure and angina. BCG is type III (thirty-third month after infarction). (B) Male, 55 years of age, with angina pectoris. BCG is type III (second month after infarction). (C) Female, aged 48, with severe angina pectoris, BCG type IV (fourteenth month after infarction).

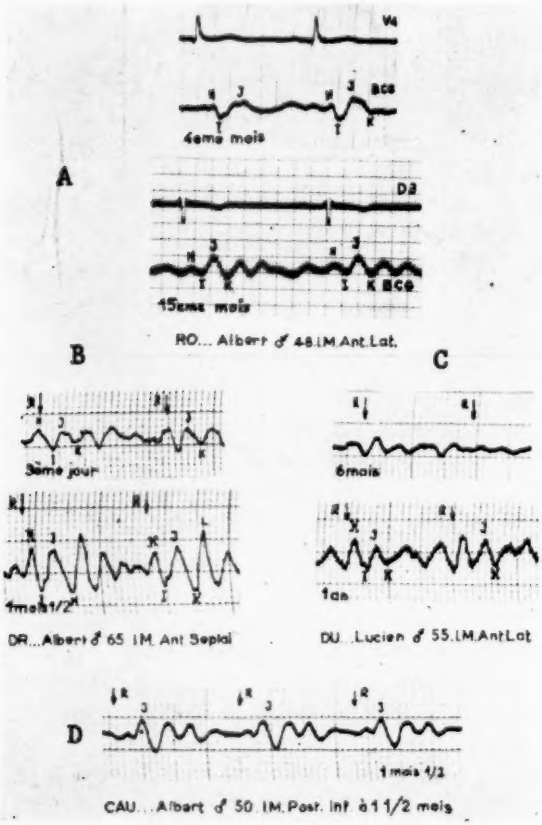
4ème mois
15ème mois
RO... Albert ♂ 48 I.M. Ant. Lat.
3ème jour
6mois
1mois 1/2
1an
DR... Albert ♂ 65 I.M. Ant. Septal
DU. Lucien ♂ 55 I.M. Ant. Lat.
1 mois 1/2
CAU... Albert ♂ 50 I.M. Post. Inf. à 1 1/2 mois

Fig. 6. Incomplete regression of the BCG abnormalities in four cases of myocardial infarction. (A) Male, aged 48, 4 and 15 months postinfarction. (B) Male, aged 65, 3 days and 1 month postinfarction. (C) Male, aged 55, 6 months and 1 year postinfarction. (D) Male, aged 50, 6 weeks postinfarction.

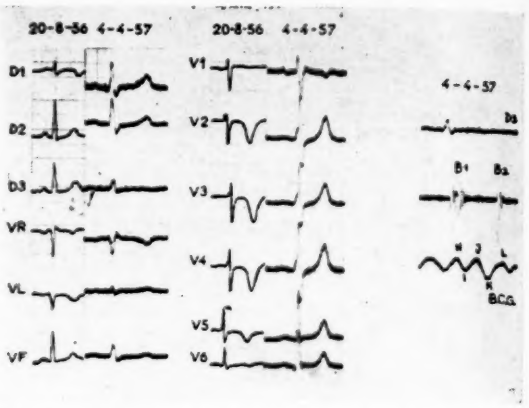

Fig. 7. Male, aged 48, with anterolateral and myocardial infarction. Concordant improvement of symptoms, ECG and BCG 8 months postinfarction.

The persistence of ballistic anomalies of type IV after the second month was noted in one of every ten cases. The severity or the duration of ballistocardiographic abnormalities is not related to the site or the date of the infarction. Nevertheless, the repetition of several crises has its effect upon the curves and upon its persistence. In every case where the tracings remained type IV the patients were functionally handicapped by some complication of the infarction; some suffered from intractable angina which prevented their every activity, and others showed signs of congestive heart failure (Fig. 5). Once and once only have we observed a case in which the ballistocardiogram tracing remained abnormal while the clinical signs were improved. In most cases serial ballistocardiograms show an incomplete improvement of the curves; in most cases the tracings returned to type II after a varying interval of evolution (Fig. 6). This improvement of the ejection force of the heart follows and coincides with improved clinical state of the patient. Only rarely do the ballistocardiogram and the electrocardiogram run a parallel course (Fig. 7 gives an example).

Practical Value of the Ballistocardiogram in Myocardial Infarction

DIAGNOSIS

As we have already mentioned, the recording of the ballistocardiogram during the acute phase has been a help in diagnosis in only very few exceptional cases. Three patients showed signs of

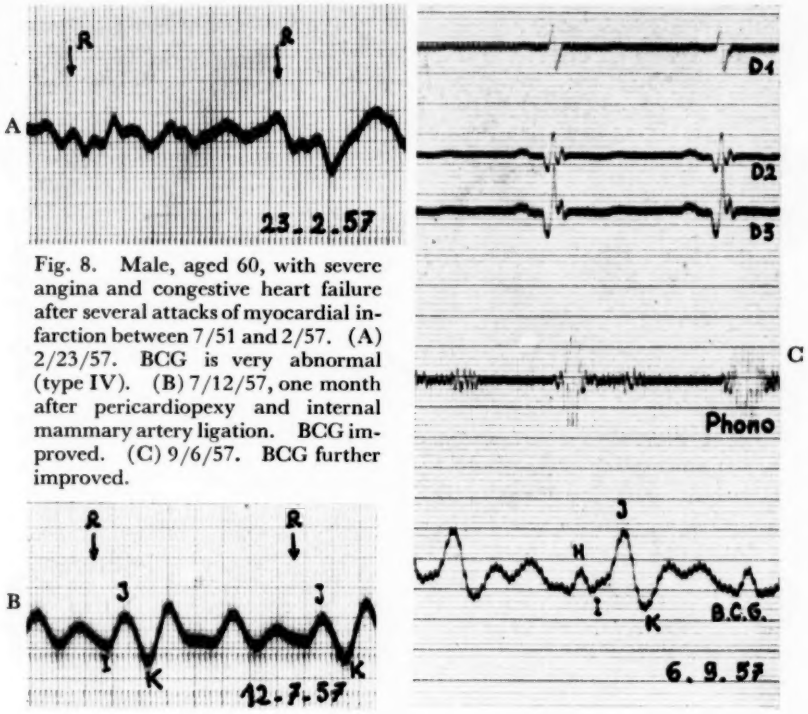

Fig. 8. Male, aged 60, with severe angina and congestive heart failure after several attacks of myocardial infarction between 7/51 and 2/57. (A) 2/23/57. BCG is very abnormal (type IV). (B) 7/12/57, one month after pericardiopexy and internal mammary artery ligation. BCG improved. (C) 9/6/57. BCG further improved.

angina without electrocardiographic changes, but a ballistocardiogram of types III and IV led us to suspect an impending infarct. The diagnosis of myocardial infarction is a clinical diagnosis, generally confirmed by the electrocardiogram. The ballistocardiogram has only documentary importance. One must consider it as a proof of the mechanical insufficiency of the heart in the face of an impending infarct.

By comparing serial ballistocardiograms after the acute episode one can follow the course of the mechanical efficiency of the cardiac muscle.[10] In any case the ballistocardiogram by itself can give no information on either the location of the infarcted area or the date of the coronary thrombosis. This information often may be obtained from the electrocardiograms.

PROGNOSIS

During the last two years many investigations have been concerned with the determination of the prognostic elements in a patient with myocardial infarct. On the basis of certain criteria, Russek and Zohman[11] divide the acute cases into "good risk cases" and "bad risk cases." Cleempoel and Enderle[12] accept the same criteria. Schnur[13,14] attributed to each complication of the acute phase a certain number of points, according to its gravity, and established a pathologic index for each case. However, the irregular evolution of the illness does not always follow such a prognostic classification, and a patient who may be accepted as a "good risk" may die before the second month has elapsed, whereas a "bad risk" may survive the acute crisis. Ballistocardiography does not bring new elements to the determination of the prognosis of myocardial infarction, for it is very seldom that the BCG grade becomes more satisfactory before the second month after the infarct.

Electrocardiographic prognosis is difficult even during convalescence. Friedberg[15] regrets that the result of an acute crisis of infarct cannot be foreseen; first, because death may be sudden and unexpected even in patients progressing favorably and, further, because it is always possible that patients who appear to be in the very last days of a fatal illness may nevertheless survive for quite a long time. Holzmann[16] and Meyer[17] believe that electrocardiograms are of some value in immediate prognosis but they hold that they have abso-

lutely no value in the long-term prognosis.

The ballistocardiogram, on the contrary, is a record of the ejection force of the ventricles due to the mechanical work of the heart. The configuration of the ballistocardiogram recorded after the second month following an acute infarct is the true indication of the permanent partial disability of the patient. In our follow-up studies of our cases of infarction we could not find any correlation between the serial ballistocardiograms and electrocardiograms. Moser *et al.*[8,9] have reported the same results. On the other hand, we have verified a very strict parallelism between the clinical course and the BCG changes in follow-up tracings.

We had four deaths. The tracings were classified as type IV in one case, advanced type III in one, and type III with very important hypokinesis in two. In one of the four fatal cases, the fatal evolution was announced by the appearance of a very atypical ballistocardiographic pattern at the time when the patient was clinically recovering.

Whenever angina pectoris occurred as a sequel of the infarction, the BCG has remained type III. It reverted to type II only when the angina improved. Moser *et al.*[8,9] found a normal ballistocardiogram in only 7 per cent of the patients who had chronic angina after infarction. In one of our patients disabled by severe angina following two successive infarcts, we found very atypical BCG patterns of Brown type IV. Following pericardiopexy with talc and ligation of the internal mammal arteries, we observed a spectacular improvement in the clinical and BCG findings, and the patient was able to increase his physical and ambulatory activity to a degree which was formerly quite impossible (Fig. 8). We do not have a sufficient number of cases operated on according to this technic to warrant definite conclusions but we personally have great faith in such surgical intervention.

Conclusion

We feel that the ballistocardiogram has an important place in the determination of the functional prognosis after an acute attack of myocardial infarction (i.e., beyond the second month). In agreement with R. and H. Mandelbaum[18] we allow the convalescing patient to resume his work when the ballistocardiogram is better than type II. Even when there are significant residual electrocardiographic anomalies, the BCG permits us to estimate the clinical evolution of the illness and to fix the date of rehabilitation of the patient. In several cases the persistence of important BCG anomalies has caused us to anticipate an untimely end when other clinical studies appeared to give hope.

The BCG supplies an objective record on which to base a conclusion concerning the prognosis after myocardial infarction. We concur with Brown and his coauthors[5,19] that the BCG should be a useful instrument for clinical evaluation of the functional working capacity and the date of rehabilitation of the cardiac patient.

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Erratum

In the December, 1958, issue (Vol. II, No. 6), the title of the article beginning on page 748 should read: Genesis of the Human Longitudinal Ballistocardiogram from the Changing Blood Distribution.

Correlation Between Serum Lipids and Resting and Exercise Ballistocardiograms

HYMAN ENGELBERG, M.D., F.A.C.C.

Beverly Hills, California

WE HAVE recently reported[1] on the relationships between the clinical diagnosis, resting and postexercise electrocardiograms, serum cholesterol, and low density lipoprotein levels in a series of 560 private patients. It was found that both lipid measurements correlated directly and significantly with the severity of the electrocardiographic findings at rest and after exercise, although there were many individual exceptions. The ballistocardiographic findings in this same group are presented in this communication.

METHODS

Briefly, since the details have been previously presented,[1] the following procedure was employed. The patients were usually seen in the afternoon and the various tests performed after the history and physical examination were completed. The ballistocardiograms were taken with the subject lying on a rigid wooden platform. A displacement type of instrument was used, a Glennite portable machine, with the tracings taken at the mid-tibial level. Although more discriminating ballistocardiographs are now available, the same instrument was used throughout since it gave satisfactory, fairly reproducible records, and the data were therefore comparable over the five to six-year period of the study. If the resting electrocardiogram was normal, and no prior myocardial infarction had occurred, a double two-step test following Master's criteria[2] was performed, and the electrocardiogram immediately recorded followed by the ballistocardiogram. Blood was subsequently drawn for the lipid determinations. Serum was analyzed for cholesterol in the office laboratory by the same method throughout the study,[3] and aliquots were mailed for ultracentrifugal determinations of low density lipoproteins.*

The two lipid parameters were determined independently. The interpretations of the electrocardiograms and ballistocardiograms were recorded on the charts prior to the laboratory report of the lipid tests. Thus, from the standpoint of the relationships between the lipid values and the cardiac instrumental tests, blind study technics were applied. The electrocardiographic interpretation followed the usual criteria. However, classification of the ballistocardiograms was more difficult since the significance of minor changes is obscure. The records were classified as normal, mild (grade 0-1), moderate (grade 1-2), and severe abnormality (over grade 2), which roughly correspond to Brown's classification[4] of grades 1-4. Abnormalities ranged from minor changes in wave form and amplitude (grade 0-1) to moderate ones (grade 1-2) and finally to records with severe distortion of all complexes. Minor respiratory variations were considered normal. No attempt was made in this study to do more than broadly define the general degree of abnormality of the tracings. It is obvious that the interpretation is a rather crude one, but there is a little evidence that more exact definition is possible in the light of our present knowledge of this modality. Despite this, the data illustrate some interesting correlations. In some cases classification of the ballistocardiograms

* Performed at the Institute of Medical Physics, Belmont, California.

after exercise was difficult because of marked respiratory motion of the body.

Results

Excellent studies have been published dealing with the ballistocardiographic findings in normal individuals, in patients with angina pectoris and myocardial infarction,[5,6] and their relation to the electrocardiographic changes in the same individuals. The results in the present series are in general agreement with those of prior publications and so will not be presented. In relation to lipids, however, apart from the statement that normal subjects under 45 years of age with abnormal ballistocardiograms have high blood fats,[6] no large series has been published correlating the two. The findings in 349 clinically normal individuals are shown in Tables I and II. Both at rest and after exercise average lipid values are higher as ballistocardiographic abnormality increases. However, the correlation of the resting ballistocardiogram with lipids is better below 50 years of age, whereas the postexercise ballistocardiogram correlates well with lipids at all ages. There were many instances, however, where elevated lipids were found when the ballistocardiogram was normal, and vice versa.

The distinct improvement in the correlation after exercise suggested an analysis of the data according to slight and marked ballistocardiographic improvement or deterioration after

TABLE I

Cholesterol and Atherogenic Index Values in Normal Individuals Grouped According to the Ballistocardiographic Findings at Rest

Age group	Blood values	Ballistocardiogram			
		Normal	Grade 0-1	Grade 1-2	Worse than grade 2
Below 50	Cholesterol (mg/100 ml)	263	284	286	299
	A.I.	75	91	93	105
	Number of cases	61	84	43	39
Over 50	Cholesterol	263	272	287	278
	A.I.	72	73	97	91
	Number of cases	11	36	40	35

TABLE II

Average Cholesterol and Atherogenic Index Values in 349 Noncoronary Patients Grouped According to the Exercise Ballistocardiogram

Age group	Blood values	Exercise ballistocardiogram			
		Normal	Grade 0-1	Grade 1-2	Worse than grade 2
Below 50	Cholesterol (mg/100 ml)	254	270	291	315
	A.I.	77	84	95	115
	Number of cases	55	73	72	27
Over 50	Cholesterol	240	250	281	302
	A.I.	61	77	87	96
	Number of cases	9	29	41	43

TABLE III

Average Cholesterol and Atherogenic Index Values in 48 Patients with Ballistocardiographic Changes after Double Two-step Test

Degree of change	Blood values	BCG better			BCG worse			Difference between means	SE
			MD	SD		MD	SD		
Slight change after exercise	Cholesterol (mg/100 ml)	262	42	40	280	46	64	18	11.7
	A.I.	82	17	24	90	26	29	6	5.9
	Number of cases	29	—	—	54	—	—	—	—
Marked change after exercise	Cholesterol	254	36	48	278	48	80	24	21.3
	A.I.	64	20	24	94	30	37	30	11.7
	Number of cases	10	—	—	38	—	—	—	—

MD—Mean deviation. SD—Standard deviation. SE—Standard error of the difference between means.

exercise, as shown in Table III. A change was considered marked when more than one grade of alteration occurred in a tracing (as from normal to grade 1-2). Slight changes in either direction were not significantly associated with lipid variations. However, there was a statistically significant difference when a marked change occurred after exercise between the atherogenic indices of those whose records improved and subjects in whom the tracings deteriorated. The low atherogenic index values found in individuals with marked as compared to slight improvement after exercise are also striking and were present in all ten subjects in whom the change occurred. These observations suggest that misleading interpretations of abnormal resting ballistocardiograms may be minimized by use of the exercise test.

Although relationships between electrocardiograms and ballistocardiograms were not an important aspect of this study, certain observations were of interest. Marked deterioration of ballistocardiographic tracings after exercise occurred in 38 subjects, in only six of whom a positive exercise electrocardiogram was also found. Ten of the 38 patients had low lipid levels and in 28 they were elevated. It is interesting that in two patients of the latter group, both of whom had negative exercise electrocardiograms, an acute myocardial in-

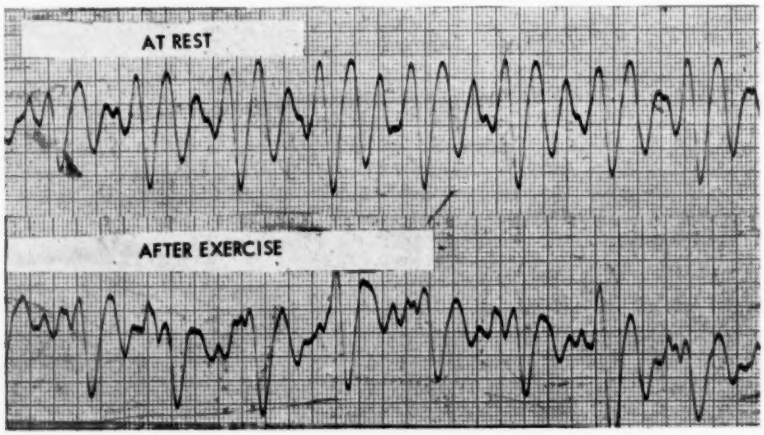

Fig. 1. Abnormal ballistocardiogram after exercise two months before an acute myocardial infarction. The electrocardiogram after exercise was normal in this case.

farction occurred within two to three years. The electrocardiographic and ballistocardiographic tracings in one of these individuals are shown in Figure 1. Both patients developed deep K waves after exercise, previously noted as an ominous abnormality by Starr.[7] While it has not been proved that marked ballistocardiographic degeneration after exercise is as significant of coronary disease as a strongly positive exercise electrocardiogram, it should nevertheless arouse suspicion and lead the examining physician to search for and correct lipoprotein abnormalities.

We have seen that marked ballistocardiographic deterioration may be found after exercise without a similar change in the electrocardiogram. The reverse may also be true when the electrocardiogram after exercise is abnormal. Thirty-two subjects had a definitely positive double Master test (at least 2 mm S-T segment depression). In nine the pre-exercise ballistocardiogram was normal to grade 1, in eight it was grade 1-2, and in fifteen it was worse than grade 2. In five of the 32 the ballistocardiogram became markedly worse after exercise, in eight it deteriorated slightly, in 16 it was unchanged, in two it improved slightly, but in one woman 45 years of age it improved from grade 2 to normal. The findings in the latter subject are shown in Figure 2. This patient was quite interesting. She complained of left chest pain, occasionally on effort. Her cholesterol was 199, the atherogenic index 33. There was no hypertension or diabetes. A hiatus hernia was found by x-ray. A consultant repeated the Master test which again was electrocardiographically positive but without pain, and he concurred in the diagnosis of hiatus hernia with possible associated coronary spasm but no heart disease. Although proof is lacking, this may represent an unusual instance in which abnormal electrocardiographic findings after exercise, if considered alone, would have led to an inaccurate diagnosis.

One further clinical observation was made during the exercise tests which is of interest. In most cases when marked electrocardiographic changes occurred after exercise, the subjects also experienced chest pain. However, marked ballistocardiographic deterioration after exercise without accompanying electrocardiographic change was usually associated with severe fatigue or dyspnea rather than pain, perhaps indicating diffuse myocardial hypoxia.

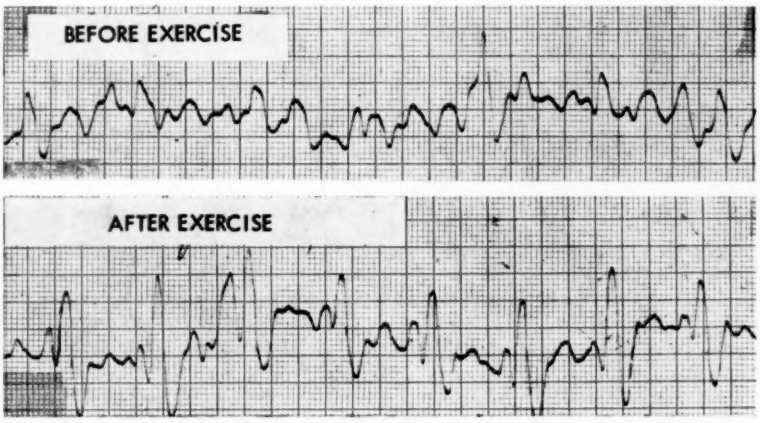

Fig. 2. Ballistocardiogram in a 45-year-old woman before and after exercise. The Master exercise electrocardiogram test was positive but the BCG shows improvement after exercise.

Comment

Quantitation of the ballistocardiogram, except for marked variations, is yet uncertain, and the record from day to day in the same individual may vary a good deal. It is therefore unwise to attribute much significance to minor variations in this test. The usefulness of the procedure is further limited by the fact that the incidence of ballistocardiographic abnormality

at rest is high for clinically normal subjects above the age of 50 years. It has therefore been suggested[5] that, in the present state of our knowledge, significance be attached to abnormal ballistocardiograms from subjects under 50 and to normal ones from those over 60. The data in Table I are in accord with that statement. The lowest lipid values are found in the older patients with normal to grade 1 records and the highest elevations in the younger group with marked abnormality. This tendency is more sharply defined after exercise, even in the older group, as shown in Tables II and III. These facts, and the occurrence of two cases of infarction in patients with previously normal exercise electrocardiograms but very abnormal exercise ballistocardiograms, indicate that the latter procedure is less deceptive than a record taken only at rest. At all ages the persistence or the occurrence of a marked abnormality after exercise, while not diagnostic of advanced coronary atherosclerosis, should suggest its probability and the need for investigating serum lipids and lipoproteins.

Summary

(1) Lipid values tended to be higher with increasing abnormality of the resting ballistocardiogram. This was much more definite below 50 years of age.

(2) Correlation of exercise ballistocardiograms with lipids was direct and significant at all ages. The lipids in individuals with marked improvement of the record after exercise were significantly lower than in subjects in whom marked deterioration occurred.

(3) Changes in ballistocardiograms and electrocardiograms after exercise are frequently not parallel. Two patients with marked ballistocardiographic deterioration and a normal electrocardiogram after exercise subsequently experienced an acute myocardial infarction. In both instances the lipid values had been elevated.

(4) In office practice the ballistocardiogram, although not definitely diagnostic of coronary disease, was useful. The finding of a markedly abnormal test at rest in younger patients, or after exercise at any age, indicates that tests of blood lipids and lipoproteins should be done.

(5) The combined application of the various modalities is useful in the earlier diagnosis of coronary atherosclerotic disease.

9730 Wilshire Blvd.
Beverly Hills, Calif.

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The Ballistocardiogram as a Predictor of Myocardial Infarction*

DeWitt Hendee Smith, M.D.
Princeton, New Jersey

Sometimes people who are otherwise apparently healthy and normal have abnormal ballistocardiograms, and then, not long after, suffer angina or myocardial infarction, or die suddenly. This sequence of events has fired the imagination of many investigators ever since it was first clearly described by Starr[1] in his first (ten-year) follow-up study on his initial normal patient series. Is the ballistocardiogram the long-sought window through which one may peer into the future? Does the ballistocardiogram display evidence of latent coronary artery disease when other methods do not? If, as indeed it certainly sometimes does, the ballistocardiogram foretells trouble when other methods fail, just how good a tool is it for this purpose? What significance should one attach to an abnormal ballistocardiogram when the history, physical examination, and other tests are all normal? And how much reassurance and comfort may be gained from a normal ballistocardiogram? Now, nearly ten years after Starr's provocative paper, there are only a few of these questions that one can answer with any certainty.

Factors Influencing the BCG

That the ballistocardiogram may be influenced by factors other than heart disease has been a complicating factor. It has long been recognized that in certain types of abnormal hearts the ballistocardiogram may be within normal limits if the stroke volume is large. Under other circumstances even the normal heart may produce a poor ballistocardiogram because of extracardiac factors. An abnormal tracing may also be produced if the patient is flabby because of lack of exercise, as indicated by Arbeit, Jokl, *et al.*[2] and supported in my own experience with highly sedentary patients. It is not as yet clear how much of the abnormality associated with advancing age is due to the fact that many old patients refrain from exercise, to the point where their ballistocardiograms show deterioration on this account rather than because of trouble in the myocardium. That tension or fatigue can also make the record look unusual is suggested in other observations.[3] While one is inclined to credit these effects to muscle tremor artifacts, it may be that they are related to the abnormalities that may be found after exercise in the electrocardiogram of psychoneurotic patients.[4]

BCG in Latent Coronary Disease

Although there is general agreement in the experience of many laboratories that prior to the development of overt coronary artery disease the ballistocardiogram may be the only frankly abnormal finding, published data to this effect are scarce. In Starr's original supposedly normal series, the 8 to 10 year follow-up[1] showed that among those over the age of 40 who had normal tracings none developed coronary artery disease. Among those whose ballistocardiograms were abnormal, however, the incidence of later coronary disease was impressively high. Currently he recalls[5] (without extensive review of his data) 20 patients in all who, after an abnormal ballistocardiogram, later developed angina or infarction, or died suddenly.

The reverse situation also occurs, though less frequently. Starr[5] cites five patients who had infarctions after a normal ballistocardiogram, and two others who developed angina.

* From the Ballistocardiograph Laboratory, New Jersey Neuro-Psychiatric Institute, Princeton, N. J. (The work of this laboratory is supported by a grant from the U. S. Public Health Service.)

Of five patients I have had who had ballistocardiograms taken before infarction, the record in four was abnormal, in the other it was normal. Starr expresses the opinion that this is about the experience of most laboratories.

An especially pertinent series is recorded by Arbeit.[6] He observed 23 instances in which patients were found to develop ballistocardiographic abnormalities not present in previous tracings. Within six weeks, 17 of these developed some other evidence of overt coronary insufficiency including acute myocardial infarction. He regards such development of new ballistocardiographic abnormality as very suggestive and advises that these patients should be very closely observed for the next several weeks.

Scarborough writes,[7] "There are some generalizations one can make. Although the ballistocardiogram is usually abnormal both before and after infarction, it may be normal in both cases. There is a strong age relationship, of course, in the incidence of abnormal ballistocardiograms and in the frequency of development of infarctions. Among our normals who subsequently developed infarctions, the ballistocardiograms were usually abnormal, but most of the subjects were over the age of 50. There were a few whose pre-infarction ballistocardiogram was normal and they were usually less than 50." This seems to state the present impressions well.

Insight into the likelihood of the ballistocardiogram being normal or abnormal in relation to coronary artery disease comes from study of data published from Scarborough's laboratory.[8] Using the cigarette test, which these investigators found correlated more closely with the coronary status than the resting ballistocardiogram or the tracing taken after exercise, tracings of normal persons were borderline or abnormal in 5 per cent below the age of 40, and in about 10 to 15 per cent of older persons. However, among subjects with known coronary disease, abnormal tracings were obtained in about 60 per cent of younger and 70 per cent of older patients. Of the older normal patients, one does not know what per cent of the abnormal tracings represented latent coronary disease and what proportion represented such factors as inactivity or tension.[2–4] In the group with known coronary disease, the effects of inactivity prescribed by physician or compelled by disease may play a large part in the production of the abnormal tracings.

The BCG and Autopsy Findings

Pathologic data are important. Blumgart and co-workers[9] showed 25 per cent of normal persons over 40 with marked narrowing in at least one coronary vessel. White, Edwards, and Dry[10] have shown much higher incidence. Their series does not distinguish on clinical grounds between normal and abnormal persons. However, they found that in their series, which was limited to men, serious narrowing of at least one, usually several, coronary vessels had occurred by the fifth decade in over 40 per cent of cases, and by the sixth decade in over 75 per cent. One may safely infer that in their series the incidence of major coronary narrowing among clinically normal men was substantial.

From these data and from experience it appears that a person with a normal ballistocardiogram may have a considerable degree of major coronary narrowing. Further, if to these are added the patients who have mural changes which are potential sites for thrombus formation but do not as yet interfere with blood flow, it may be understood why myocardial infarction may occur in patients whose ballistocardiograms are not abnormal.

The BCG and Blood Lipids

Recently the level of the serum lipids has received much attention as indices of what may be happening in the coronary and other arteries. The evaluation of these factors has proved so vexing that a large study from four laboratories[11] was undertaken to try to settle the point. Of nearly 5,000 men between the ages of 40 and 59, working and supposedly healthy, and followed for one or two years in this study, some 82 developed manifest infarction or other evidence of coronary insufficiency. If the series is divided at the 50 per cent or median point in reference to the blood cholesterol levels, there were significantly more with high than with low blood cholesterol who came down with coronary disease, but if the division is at the 75 per cent point, the significance is lost. This seems to be somewhat less useful than the ballistocardiogram, in that although an elevated cholesterol is likely to be a precursor of coronary disease, exceptions are extremely numerous.

Conceivably, combined use of the ballistocardiogram and the serum cholesterol may well improve the prediction value, but to this also there are likely to be exceptions.

Conclusions

In brief, the abnormal ballistocardiogram sometimes predicts myocardial infarction or coronary insufficiency when other methods fail, but exceptions are so numerous that its value is statistical rather than individual. Sudden advent of an abnormal ballistocardiogram in an individual whose tracing was previously normal may prove to have significant statistical importance. At present, we do not have the statistics on which to say just how good the method is in this respect.

What seems to be indicated to make a quantitative evaluation of the ballistocardiogram as a predictor of coronary disease is a study comparable to that referred to for the blood lipids. Many of the needed data no doubt exist in the records of some of the larger laboratories, and Starr[5] has indicated that in the next years he will undertake such a study of his material. Scarborough and his colleagues[7] have such a study under way. Scarborough indicates that large numbers and long follow-up periods are needed. Starr's 20-year follow-up of his original normal series will add data. But much of the work may have to be projected, including correlations with the lipids. One hopes that five years from now it will be possible better to evaluate just how much importance may be attached to the ballistocardiogram when it is normal and when it is abnormal, and how good it may be as a predictor of myocardial infarction. At present, we do not know.

Summary

(1) The ballistocardiogram may be the only abnormal finding in persons who later develop myocardial infarctions. However, especially in younger persons, it may be normal both before and after an infarction.

(2) Factors other than coronary disease may be important in the genesis of an abnormal ballistocardiogram. Lack of exercise and tension or fatigue are among these factors.

(3) Considerable further work will have to be done to evaluate the role of the ballistocardiogram as a predictor of infarction in the absence of other signs of coronary disease. Comparisons with blood lipid levels will be of interest.

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Case Report

Treatment of Intractable Congestive Heart Failure

Report of Two Cases Benefited by Utilization of the Sump Phenomenon*

EUGENE B. LEVIN, M.D. *and* ISRAEL KLEIN, M.D.

Los Angeles, California

THORACENTESIS has been used in congestive heart failure, primarily for relief of lung compression.[1–3] Schemm and Camara[4] pointed out that repeated use of thoracentesis and paracentesis in cases of refractory edema due to heart failure, nephrosis, and cirrhosis will greatly relieve such patients. Their studies with deuterium oxide (D_2O) and repeated chest x-rays showed that such procedures mobilized and eliminated peripheral edema without affecting the serum sodium or protein levels. Review of the literature and recent textbooks[5–7] reveals little emphasis of this method in the treatment of intractable congestive heart failure with pleural effusion and severe peripheral edema. These cases are reported to show the encouraging results from using this procedure.

CASE HISTORIES

CASE 1. C. E. J., a 67-year-old female, suffered from obesity and hypertension for 25 years. About eleven years ago she first developed congestive heart failure which was treated with digitalis, a salt-free diet and repeated mercurial injections. As a result of her illness she gradually lost 140 pounds. From 1952 until the time of her first hospitalization in 1955, she was practically bedridden, unable to do any of her household chores, because of shortness of breath on exertion, episodes of nocturnal dyspnea, orthopnea, and massive edema of the entire lower portion of the body.

Physical examination during most of this time revealed rales at both lung bases, an enlarged heart with a grade 3 systolic murmur at the apex, hypertension varying from 220/90 to 250/120, hepatomegaly and 4+ pitting edema of the ankles, legs, and presacral area. She required 2 or 3 mercurial injections a week and the response varied greatly (Fig. 1). In September, 1954, she developed the first signs of a right pleural effusion. This cleared spontaneously at first, but by December her condition had worsened. The effusion increased, the peripheral edema was more pronounced, and a complete heart block appeared which was felt to be the result of digitalis toxicity.

In January, 1955, the first thoracentesis was performed with only slight relief. Two months later this was repeated with the same results. One month later, she was hospitalized and three more thoracenteses were performed with marked success (Fig. 2). The peripheral edema cleared completely and the pleural effusion did not recur. On admission to the hospital the serum sodium was 150 meq and the chlorides were 101 meq.

Since discharge, the patient has remained improved and she has been able to lead a more active life. She has been maintained on digitalis, a low-salt diet and mercurial diuretics every one to two weeks. There has been no recurrence of the massive edema or right pleural effusion for over two years.

CASE 2. E. F., a 54-year-old female, suffered an acute anteroseptal myocardial infarction on July 8, 1953. She was hospitalized for five weeks, during which time she developed congestive heart failure. When first seen by us, she was on maintenance digitalis and there were no signs or symptoms of congestive heart failure. However, periodically she would have bouts of severe left heart failure. The first was in November, 1954. She

* From the Department of Medicine, Cedars of Lebanon Hospital, Los Angeles, California.

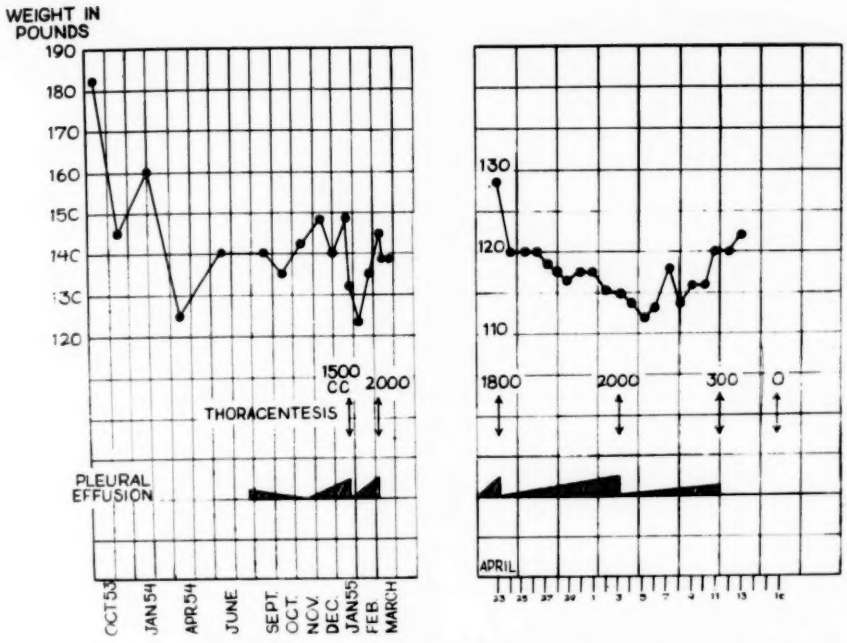

Fig. 1. Case 1. Clinical course showing relationship between weight, pleural effusion, and thoracenteses.

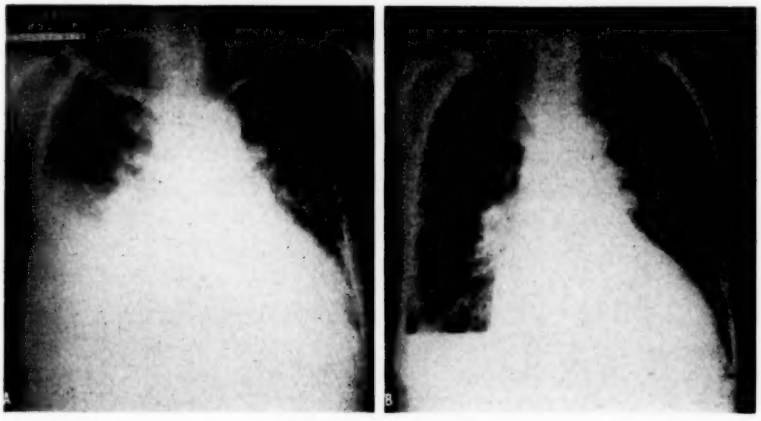

Fig. 2. Case 1. X-rays of the chest before and after thoracenteses.

responded rapidly to mercurials and bed rest. Fluoroscopy at this time revealed a markedly enlarged left ventricle with a general ballooning out of the left ventricular wall, and some right pleural effusion. In December, 1955, during a similar episode, edema of the legs and hepatomegaly were first noted.

In February, 1956, she became ill with virus pneumonia and developed severe congestive heart failure with rales at both lung bases, hepatomegaly with the liver edge 5–6 cm below the right costal margin, and ankle, pretibial, and presacral edema. She was hospitalized and made a prompt recovery on rest and mercurials, losing 11 pounds in five days. Following this episode, the liver remained enlarged, the ankles continued to swell by evening, and the patient complained of more dyspnea on exertion. She was seen more often and kept under relative control with frequent mercurial injections.

In November, 1956, she was hospitalized because of persistent abdominal pains, hepatomegaly, right pleural effusion and ankle edema. Gastrointestinal x-ray series was normal and the patient lost 10 pounds on bed rest and mercurials alone and felt much better.

At home she did poorly again, the peripheral edema increased, and there was no longer any response to mercurials. She was hospitalized in January, 1957, because of extreme shortness of breath, marked weakness, and excessive swelling of her abdomen and legs. Examina

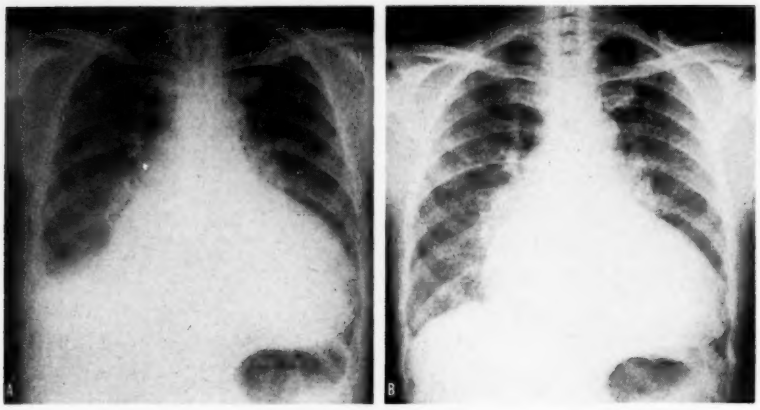

Fig. 3. Case 2. X-rays of the chest before and after thoracenteses.

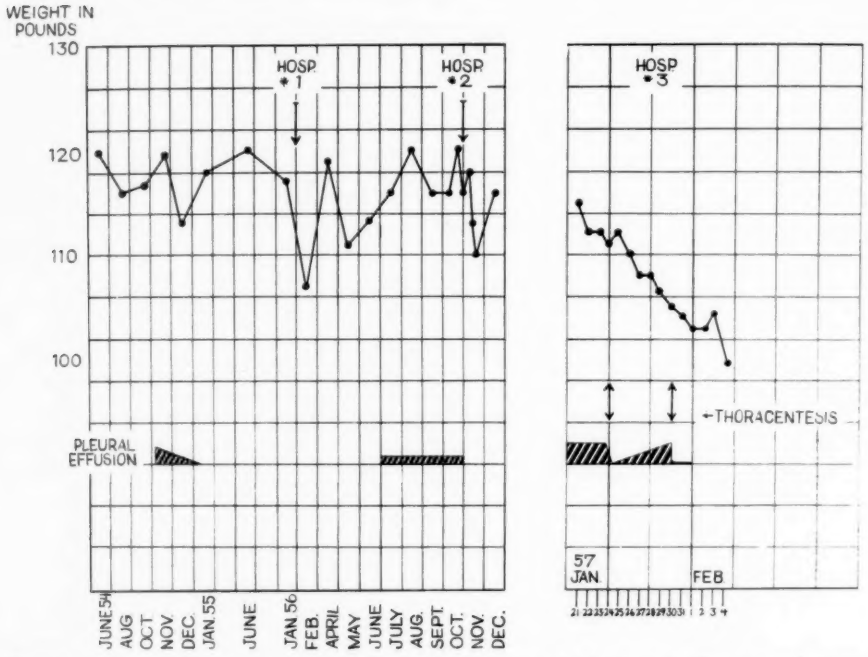

Fig. 4. Case 2. Graph showing relationship between weight, pleural effusion, and thoracenteses.

tion at this time revealed a right pleural effusion (Fig. 3), tender, enlarged liver, and 4+ pitting edema of the ankles, lower legs, thighs, presacral area and abdominal wall. Two thoracenteses produced a total of 1,500 ml of fluid. All of the peripheral edema disappeared rapidly and the response to the mercurial injections was restored (Fig. 4). The blood urea nitrogen and serum electrolytes were within normal limits when she was hospitalized.

From February, 1957, until last seen in November, 1957, she has been feeling fine (despite the fact that her husband was killed in an accident) and has had no recurrence of symptoms, no right pleural effusion, no peripheral edema, and has needed no further mercurial injections.

Comment

The disappearance of the peripheral edema and pleural effusion and the general clinical improvement were dramatic and rapid in both patients. The causes for the refractoriness to the usual regimens were not apparent (both patients had normal electrolyte patterns prior to treatment). Patients under these circumstances have many and intense stimuli directed toward the renal tubules, and to eliminate sodium and water via the kidneys is impossible. Repeated thoracentesis bypassed the

kidney and acted as a sump phenomenon.

A sump, a term first used in mine engineering, is defined as an area into which liquids drain by gravity, i.e. from higher to lower areas. In the interval between pleural aspirations, the fluid of the interstitial spaces seeps readily into the sump from which edema fluid has been taken.[4] The changes in body weight may not be remarkable but the peripheral edema disappears. It would be hard to say, without further clinical and physiologic investigations, what the exact mechanisms for these responses were. Probably changes in intrathoracic pressures draw the fluid into the pleural space where it is easily removed, thereby increasing cardiac function and mechanically improving the failing circulatory system. Thereafter, normal defense mechanisms against failure, including the renal responses, are able to take over.

In congestive heart failure when pleural effusion is encountered together with peripheral edema and refractoriness to the usual therapeutic regimen, we urge the use of repeated thoracentesis.

Conclusion

Two cases of refractory heart failure with right pleural effusion and massive peripheral edema were treated with repeated thoracentesis, utilizing the sump phenomenon, with excellent results. The exact mechanism is not too well understood and awaits further studies. However, the use of this regimen in cases of intractable heart failure is strongly urged.

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Coming in the March issue . . .

Treatment of Cardiac Arrhythmias . . . Reviews on Extrasystoles *and* Atrial Fibrillation and Flutter . . . Angina Pectoris: Origin of ST Deviations . . .

Historical Milestones

Early Impressions of Mediate Auscultation by James Clark (1819)

SAUL JARCHO, M.D.

New York, New York

IN THE YEAR 1819 Laennec issued the first edition of his immortal *Treatise on Mediate Auscultation*, a work which not only introduced a basic technic of clinical diagnosis but also established the diagnostic characteristics of almost the entire range of pulmonary diseases. Laennec's innovation made it possible for the physician to recognize with satisfactory precision the nature and extent of thoracic disease *during the lifetime of the patient*. Although Laennec was not without his detractors, his work for the most part was favorably received by the medical profession in France and elsewhere.

In the same year, 1819, a young Scottish physician named James Clark was traveling in Europe. He had come first, during the previous year, to the south of France and to Switzerland in order to accompany a tuberculous patient and to gather information on the effect of climate. In 1819 he was in Paris and seized the opportunity to visit the hospitals and study the medical scene. Having arrived not long after the publication of Laennec's book, Clark was able to observe something of the impression which that work had caused. It is this which gives his observations much of their freshness and value.

Clark completed his travel notes in 1819. They were published at London in 1820 under the title of *Medical Notes on Climate, Diseases, Hospitals, and Medical Schools, in France, Italy and Switzerland.** An amplified edition was published in 1829 with the title *The Influence of Climate in the Prevention and Care of Chronic Diseases.*

Clark subsequently enjoyed a distinguished career in medical practice. He became physician to Prince Leopold, later King of Belgium. Subsequently he was physician-in-ordinary to Queen Victoria. He was made a baronet in 1837. He died in 1870.

* * *

JAMES CLARK'S OBSERVATIONS

The following notes on the Hospitals of Paris, as well as the others to be submitted to the reader, were taken merely for my own information without the smallest intention of publication. The only hope I have of their being well received, is that, as far as I know, they contain the only remarks published on the present state of the medical practice of these hospitals, and that therefore, imperfect as they are, they are better than none.

All the hospitals of Paris are under the direction of a general administration, and from the office of this board, where medical men attend during a certain part of the day to examine them, patients are sent to the different hospitals. This plan may be attended with some inconvenience to the patients, but has not a few advantages for the practice of medicine.

Through means of this arrangement the physician of any hospital, whose attention is turned more particularly to any disease or class of diseases, by application to the office of central administration, may have such diseases sent to his own hospital. Thus a much greater number of cases of the disease, which is the

* The excerpts which follow are taken from pp. 127–8 and 153–9.

object of his particular enquiry, is brought under his observation in a given time (an object of no small importance) than could otherwise, or might indeed ever have been. To this plan, perhaps we owe, in a great measure, the excellent works of Corvisart and Bayle, who were both physicians of La Charité, which is now, indeed, almost entirely set apart for chronic cases. To the same circumstance more lately are we indebted for the excellent work of Dr. Laennec on the diagnosis of the diseases of the chest . . . .

HÔPITAL NECKER

Close to the Hospital I have described is that endowed by the wife of M. Necker the celebrated minister of state. It is a small hospital containing about a hundred and thirty patients; but from being the one in which the late experiments of Dr. Laennec on the diagnosis of diseases of the thorax were made, I visited it frequently with the view of ascertaining the utility of his method. Dr. Laennec was indisposed, but his colleague Dr. Cayol pointed out to me several cases where the information gained by the application of the *sthenoscope* was useful in ascertaining the nature of the disease. I found, however, that it would require more time than I had to bestow to make myself fully acquainted with the use of this instrument. Nevertheless I observed enough to convince me that much useful information is to be acquired through the medium of this instrument in distinguishing the disease of the different viscera of the thorax.

The instrument used by Doctor Laennec for this purpose is a perforated cylinder of wood about thirteen inches long, the perforation being about four or five lines in diameter; it is divided into two parts and scooped out at one of the extremities. When used, one end is applied to the chest of the patient and the ear of the physician to the other, and from the peculiar sound communicated through the medium of the instrument, while the patient is speaking, or breathing, or by the pulsation of the heart, the physician is enabled to ascertain the nature, and often the extent of the disease more accurately than has hitherto been done by any other means. Several medical men in Paris, I found, thought highly of this new method, and the report of the Institute is very favourable. Dr. Récamier, in particular, one of the physicians of the Hôtel Dieu, informed me, whilst going round his wards, that he could accurately discover the extent of injury in most diseases of the lungs by means of the cylinder, which he carried constantly in his hand.

It has been asked in reference to Dr. Laennec's discovery, what it will avail us to know the exact situation of an ulcer in the lungs, or whether it is a little larger, or smaller than we believed?—whether we shall be better able to cure an organic affection of the heart or large blood vessels, by knowing the particular part affected? The remark is futile, and has a tendency to check philosophic research. To know the nature and extent of a disease is surely the first step in our progress to the adoption of rational means of cure; and though the diseases particularly alluded to, are, unfortunately, beyond the known powers of medicine, the profession has not assuredly arrived at that degree of perfection to entitle us to pronounce that they will always remain so. But setting aside other advantages, it must surely be highly satisfactory to every ingenious mind to know the exact nature of the disease under which a patient labours, even when it is known to be incurable. How often the mind of the physician is lost in vague conjecture throughout the whole progress of some of the diseases alluded to, experience can best tell.

It is also sometimes of much importance to be able to give an accurate prognosis of a disease which is incurable; and this can often only be done by a knowledge of its extent, of which the symptoms generally relied on, are so often a fallacious indication. Among the consumptive cases which I lately met with abroad, I have had frequent occasion to remark how widely some of our best practitioners have erred in foretelling the termination of a disease; a proof, not of ignorance, but that the symptoms usually trusted to are insufficient even to guide the most experienced in their prognosis. I had lately a case under my charge which excited much interest, where, from the closest attention to all the symptoms, no physician would have been warranted in

giving the prognosis which the ultimate result of the case showed to be the correct one. Had I been acquainted with Dr. Laennec's method (not then published) I could have ascertained the extent of disease in the chest which the usual symptoms did not indicate, and could thus, at least, have been enabled to prevent much inconvenience, and perhaps the rise of hopes which were to be soon blighted.

In consultation with some other medical men, I witnessed the case of a Piedmontese at Rome, who was supposed to labour under some extensive organic disease of the heart or aorta. In this case the palpitation at times was extremely violent and the dyspnoea very great. Little had been done before we saw this patient, and the remedies used afterwards had only the effect of mitigating the symptoms for a time. General dropsy soon appeared, and the patient, as frequently happens in such cases, died of apoplexy. On examination after death the only unusual appearance about the heart was a slight enlargement of that organ; the pericardium contained much serum and the chest on both sides was filled with the same fluid, the lungs being greatly compressed. Had the nature of this poor man's disease been known at the beginning, there is no reason to believe that his life might not have been prolonged, perhaps for years.

This was one of those numerous cases where affections of the mind appear to produce not only functional but organic disease of the heart. This man had been reduced by the late political changes, from a captain in the French army to the menial office of a waiter in an hotel, while he was, at the same time, an exile from his native land where his property had been confiscated. The chagrin produced by this reverse of fortune he could never get the better of, and I have no doubt that it was the cause of his disease, since late observations have amply shown that the old and ridiculed idea of dying broken-hearted is often but too true. The above case shows, at any rate, that we should not rashly reject any means that may be pointed out of increasing our diagnostic knowledge of such important diseases; and if Dr. Laennec's discovery supports the character given of it, he has conferred an essential service on his profession and mankind in general, and deserves their grateful thanks;—however the more easy-minded part of the profession may smile at the means he uses.

To give an account of the manner of using the Sthenoscope does not come within the intention of this Essay, and this is of the less consequence as I have reason to believe a full review of that and of the other parts of Dr. Laennec's valuable work will appear in an early number of Dr. Johnson's Medico-Chirurgical Review.*

In all diseases of the chest much attention is also paid in Paris to the information to be gained by means of percussion of the cavity by the hand, a means of information which is little if at all attended to, I believe, in England. A patient brought into any of the hospitals of Paris with any affection of the chest, is as regularly submitted to this process as the English physician would ascertain the state of his pulse; and the high opinion that is entertained of this as a diagnostic in France cannot be more strongly evinced than in the following encomium bestowed on it by the physician above mentioned, who has necessarily given great attention to the investigation of diseases of the Thoracic viscera: "Percussion of the chest according to the method of the ingenious observer whom I have just cited [Auenbrugger] is indisputably one of the most valuable discoveries with which medicine has ever been endowed. It has subjected to direct judgment of the senses many diseases which hitherto had been recognized only by general and equivocal signs and has made their diagnosis certain and easy." (Laennec, R.T.H.: De L'auscultation médiate . . .Paris, 1819, p. 4).

* * *

* An English Physician to whom I gave a sthenoscope which I brought from Paris with me, informs me he has already found it useful in the diagnosis of some of the diseases of the heart. [Footnote by Clark.]

Evaluation of an Abdominal Continuous Murmur

ALFREDO BUZZI, M.D.

Buenos Aires, Argentina

HISTORY

The patient, a 60-year-old white male, complained of a dull and continuous pain in the right iliac fossa of 12 days' duration, initially accompanied by nausea, cold sweats, and a fainting sensation. Pain persisted for 4 days, diminishing progressively in intensity, but a week later severe pain in the right iliac fossa reappeared, this time radiating to the epigastrium and both lumbar regions. It was continuous and noncolicky. Fainting and profuse sweating recurred.

PHYSICAL EXAMINATION

The patient was thin and obviously anemic. He was in acute distress, complaining of severe abdominal pain. There was pallor of the skin and mucous membranes. Cold sweat covered the face and hands. The heart rate was 120 per minute, blood pressure 100/70 and respirations 30 per minute.

Relevant physical findings were confined to the abdomen. Inspection revealed diminished respiratory excursion and an umbilical pulsation synchronous with the femoral pulse. Palpation was very painful, particularly on the right side and in the right lumbar fossa. In the umbilical region there was a hard, orange-sized tumor showing expansile pulsations. With the stethoscope placed over the tumor, a continuous murmur with systolic accentuation was heard, of moderate intensity and without propagation.

CLINICAL COURSE

Morphine was given for pain, and a transfusion of 500 cc of blood was administered for replacement of blood loss. It was considered that the patient had a ruptured abdominal aortic aneurysm, probably of atherosclerotic origin. This diagnosis was based on the presence of a pulsating abdominal mass in an elderly male who was acutely anemic and in shock. The previous painful episode was interpreted as indicating a former and incomplete tear of the aortic wall. The continuous murmur over the tumor was considered evidence of a fistula between the aortic aneurysm and an abdominal vein, most likely the inferior vena cava.

A grafting operation was planned, and supportive therapy was attempted while the vascular surgeon was called. However, the patient died two hours after admission.

NECROPSY

Abundant blood clots were found in the retroperitoneal space. The abdominal aorta was dilated from the inferior mesenteric artery to its bifurcation in the common iliacs and was adherent to the inferior vena cava. The aortic aneurysm measured 4 cm in its maximal diameter. Opening of the aorta revealed numerous atherosclerotic plaques with calcification, some of them ulcerated. A fistulous orifice was present in the aortic wall, permitting the free passage of an index finger. The fistula communicated directly with the inferior vena cava, which also showed a recent posterior tear (Fig. 1).

Histologic study of the aortic wall demonstrated medial sclerosis, subintimal deposition of fat, and organized thrombosis (Fig. 2).

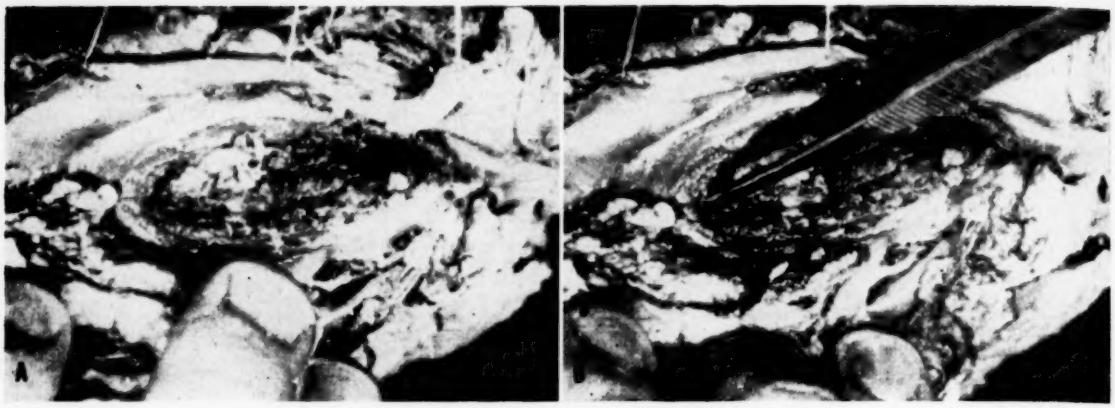

Fig. 1. (A) The specimen constituted by the affected segments of the aorta and inferior vena cava. The vein has been longitudinally opened. The orifice of the arteriovenous fistula can be seen. (B) Forceps introduced in the fistulous orifice.

The pathologic diagnosis was arteriosclerotic aortic aneurysm with rupture into the inferior vena cava and the retroperitoneal space.

Comment

Aneurysm of the abdominal aorta of arteriosclerotic origin is an increasingly common condition in our aging population. Recent development of arterial graft surgery permits the resection of the diseased segment and the reconstruction of the vessel's continuity. This makes the clinical diagnosis of this process of practical importance. Although during its chronic phase the aneurysm produces a distinct clinical picture, which can be confirmed by abdominal aortography, its rupture may simulate an acute abdominal condition if a pulsating mass is not detected.

The aneurysmal sac grows progressively, and its commonest complication is a tear of its wall, with hemorrhage into the retroperitoneal space, and occasionally into the duodenum or ileum. Perforation into the inferior vena cava is of exceptional occurrence. The clinical course following rupture depends on the size of the fistula, the cardiac reserve, and the extent of further laceration. There may occur either massive edema of the lower extremities, with venous collateral circulation on the abdominal wall, or a sudden collapse with diffuse abdominal or lumbar pain. In both instances a continuous murmur over the umbilical region and signs of a pulsating and expansile tumor will permit the diagnosis of this uncommon complication of aneurysm of the abdominal aorta. The present case illustrates the importance of not limiting the stethoscope's area to the chest.

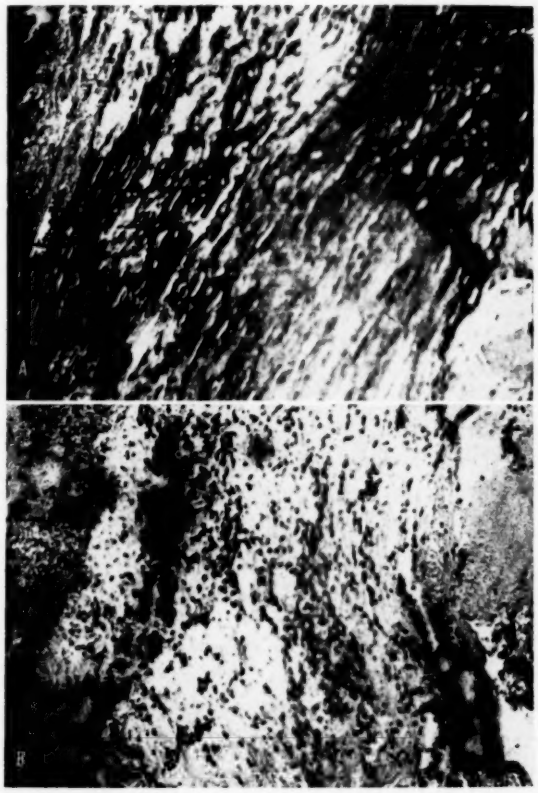

Fig. 2. (A) Histologic section, showing atheromatous aortic wall. (B) Histologic section, showing inferior vena cava with recent thrombosis and thickened wall.

Pueyrredón 615
Buenos Aires, Argentina

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Relation Between Cardiac Failure and Gastric Ulcer in the Older Age Groups

DURING a five-year observation period, Drs. Michael M. Klein and Eugene L. Walsh (Veterans Administration Hospital, Huntington, W. Va.) noticed that gastric ulcer occurs mainly in the older age group (*Radiology* 70: 672, 1958). They found that out of the 1,187 cardiac patients, 115, or 31 per cent, had gastric ulcers. This is an over-all percentage. Examination of the cardiac patients in acute failure showed that 28 per cent had a gastric ulcer. The incidence of gastric ulcer was the greatest between the ages of 50 to 60, with 27.7 per cent, and between 60 and 70, with 50.4 per cent. Over 70 and under 50 it was less than 10 per cent. Another interesting observation was that the ulcer was most common in congestive heart failure (42 per cent); in coronary heart disease the incidence was 31.2 per cent, and in arteriosclerotic heart disease without failure 28.3 per cent.

Several cases were observed over a period of years. During this period, the patient often came into the hospital primarily for cardiac failure and was found to have melena, or came in for gastric hemorrhage and was found to have cardiac failure. These patients on cardiac management improved roentgenologically, and the ulcer disappeared. However, each time these patients developed cardiac failure again, the ulcer recurred simultaneously. Another interesting observation was that no gastric ulcer was found among the cardiac failure patients in whom the failure was secondary to valvular heart disease.

These findings seem to contradict the previous belief that indigestion in cardiacs is caused by digitalis and also that the gastric ulcer is potentially malignant and should be operated.

Sodium Restriction in Experimental Renal Hypertension

THE MECHANISM by which restriction of dietary intake of sodium often results in lowering of blood pressure in hypertension is obscure. Several types of experimental hypertension in the rat are associated with an increased content of sodium and potassium in the aortic wall. The demonstration that the renal arteries of hypertensive patients contain an increased amount of sodium suggested that the effect of a diet low in sodium might be to reverse this "chemical lesion." Therefore, studies were undertaken by Drs. Paul D. Redleaf and Louis Tobian (Department of Medicine, University of Minnesota Hospitals, Minneapolis, Minn. (*Circulation Res.* 6: 343, 1958) to delineate the relationships between dietary intake of sodium,

compositional changes in the aorta, and blood pressure in hypertensive rats.

Rigid restriction of dietary sodium resulted in a modest reduction of blood pressure in rats that had one renal artery constricted, with or without removal of the opposite kidney. Only when dietary sodium restriction was begun early could a statistically significant lowering of blood pressure be demonstrated. A significant reduction in the amount of extracellular sodium in the aorta occurred as a result of such a diet. However, they could not demonstrate a significant change in the potassium content or the Na:Cl ratio, both of which are characteristically elevated in experimental hypertension. The fact that restriction of dietary sodium did not greatly alter intracellular sodium or potassium may be related to its limited efficacy in lowering blood pressure.

Experimental renal hypertension can actually develop despite the most rigorous restriction of salt intake begun before operation. This demonstrates that dietary sodium intake plays no more than a secondary or enhancing role in the pathogenesis of this type of hypertension.

A decrease in the blood pressure of hypertensive rats as a result of the administration of reserpine can be correlated with a decrease in the previously elevated amount of potassium in the wall of the aorta. This is further evidence that compositional changes in the hypertensive aorta are intimately associated with the level of arterial blood pressure. If similar compositional changes occur in the walls of arterioles, they might modify arteriolar resistance by altering smooth muscle tone. Furthermore, an increase in total cation (sodium plus potassium) content must be accompanied by an increased amount of water in the arterial wall. Such a "waterlogging" effect might, by itself, account for the increased peripheral vascular resistance in hypertension.

Workmen's Compensation for the Cardiac

Relationship of Work to Heart Disease

LOUIS H. SIGLER, M.D., F.A.C.C.*

Brooklyn, New York

IN A recent communication[1] a short outline was presented of a survey made by the New York State Workmen's Compensation Board on the possible relationship of strain to cardiac disability. The survey consisted of a questionnaire sent out by the Board to a number of cardiologists and internists with reference to the problem, and the answers received. I stated in that communication that each question would be taken up by members of our Committee for careful scrutiny and discussion and would be presented in the Journal from time to time.

The first question the Board asked was: "In your opinion, can work to which a man is normally accustomed over a period of years and involving no unusual physical exertion produce heart disease in the workman?" Of 381 replies received 89.7 per cent said *no*, 4.2 per cent said *no with some exceptions*, 1.5 per cent said *yes*, and 1 said *possibly*. The conclusion of the Board was that "there is no substance to the fiction that work can lead to any type of heart disease."

I submitted this question and the response to each member of our Committee for study, expressing my feeling that the question was too general to warrant a proper answer. Three members had a similar opinion but offered no discussion of the problem. One of the replies received from Dr. I. Robert Frank of Boston was very interesting insofar as he discussed to a considerable degree the entire problem of compensation in cardiac disability due to strain but did not specifically cover to any extent this individual question. I have therefore thought it important to discuss personally this important problem in this communication. Inasmuch as the views expressed are my own, our Compensation Committee cannot be held responsible for them. I offer these views with the hope that they will stimulate further discussion and investigation of the problem.

MEANING OF THE QUESTION

Before discussing this question we must clearly define its meaning. As submitted, the question was evidently attempting to get an opinion about whether ordinary physical but not unusually exertional work over a period of years will produce pathologic changes in the heart. In preparing this question the Board made sure to exclude heart disease caused by certain occupational hazards such as "overexposure to various dust offenders" which might first lead to pneumoconiosis, silicosis, or berylliosis and subsequently to the development of cor pulmonale, or exposure to various gases or chemicals which might secondarily affect the heart. We must therefore confine our discussion to occupational pursuits which exclude these hazards.

TYPE OF CARDIAC DISEASE UNDER DISCUSSION

Before we can logically tackle this problem we must have a clear understanding of what diseases of the heart we must look for in the course of occupational pursuits and the kind of occupations which may predispose to such disease. Furthermore, we must clearly under-

* Chairman, Workmen's Compensation Committee, American College of Cardiology.

stand that the effects of the occupational pursuits may occur slowly over a period of years before they may be recognized subjectively and objectively. Any occupation which suddenly throws an unusual burden on the heart, resulting in cardiac failure recognized clinically, is necessarily of an acute nature and does not belong to this question. Also, it is doubtful whether myocardial disease will develop *per se* even after prolonged work of a moderately physical nature. In fact, it is fairly well established that physical work is beneficial to a normal heart, and graduated, well-controlled activity may also be of benefit in some form of heart disease.

The only disease state that may develop stealthily in the heart over a period of years is coronary atherosclerosis, and here the etiology is far from established. Although there are undoubtedly a great many etiologic factors operating in the development of the disease, work of any kind cannot be excluded as one of the factors, as will be shown later. We must realize, of course, that coronary atherosclerosis up to the stage when acute manifestations develop cannot truly be considered heart disease. It is only when the process has reached a stage at which it interferes with the blood supply to the heart, resulting in transient or permanent ischemia of the myocardium with or without necrosis, or when a sudden severe acute episode occurs which completely occludes a coronary vessel that we recognize the condition. The problem we must solve then is whether occupational pursuits enter into the pathogenesis of coronary atherosclerosis, and also, what occupational pursuits contribute most to the production of this disease state.

Possible Causes of Coronary Atherosclerosis

It must be admitted that with our present knowledge of the causes of coronary atherosclerosis these questions cannot be definitely answered. No person, however, no matter how expert a cardiologist or internist he may be, can say with certainty that prolonged work over a period of years does not in any way contribute toward the development of the disease. The reason is that no investigation of the problem is possible in the laboratory, where all experiments are necessarily acute and no duplication can be made of the slow development of the disease over many years that occurs in the human.

My personal feeling is that work of any kind, particularly indoor work, is one of the long-term contributing causes of the disease. This appears to be substantiated by the fact that the disease is most prevalent in highly industrialized parts of the United States and the world over.[2, 3] We must recognize, however, the fact that many factors in life outside work are also operative. Thus, heredity; the hurried life of our modern civilization; overindulgence in food, alcohol, and tobacco;[4] insufficient relaxation and open air life, all undoubtedly have some causative effects. Metabolic changes, particularly disturbances in lipid metabolism, are most likely important causative factors. This has received the greatest amount of investigation in recent years. As a result there appears to be the belief that a disturbance in lipid metabolism is the only cause of coronary atherosclerosis. It is based on the invariable findings of cholesterol and fat deposits in the atheromatous plaques of the coronary vessels. However, the fact that such deposits are absent in the early degenerative areas of the coronary vessels, as shown by Moon and Rinehart,[5] would speak against a disturbance in fat metabolism as the sole initiating cause. Fat and cholesterol seem to deposit, for as yet unestablished reasons, in areas which are already the seats of some degenerative changes. In the later stages there is also a deposition of calcium which is certainly not part of disturbance in fat metabolism.

There is also a school of thought that considers the development of coronary atherosclerosis as a "natural aging process." This idea certainly has no scientific basis. Atherosclerosis of the coronary vessels has been observed as early as the first decade of life by Moon and Rinehart and other observers before them. Enos and co-workers,[6] in a study of 300 autopsies of men 18 to 48 years old killed in the second World War, found evidence of a greater or lesser degree of coronary atherosclerosis in as many as 77.3 per cent of cases. These findings together with the facts that many individ-

uals far advanced in age are free from the disease and that the atheromatous process is patchy in its distribution would tend to speak against "aging," whatever it means, as the cause of the disease. The reason why the greatest involvement of the pathologic process in the vessels occurs in the older age groups is that there was more time given to the causative factors to produce the disease.

Pathogenesis of Coronary Atherosclerosis

The pathogenesis of coronary atherosclerosis has not as yet been established. From the nature of the pathologic changes in the coronary arteries and from some knowledge of the hemodynamics of the coronary circulation we may form an idea as to the pathogenesis of the disease.

Atherosclerosis of the coronary arteries, like that of other arteries of the body, is patchy in distribution. The early phases are characterized by patchy fibrous degeneration of the intima. This is followed by tissue reaction, with cellular infiltration and vascularization of the involved areas. According to Paterson,[7] vascularization takes place in the form of capillary outgrowth from within the lumen of the coronary artery. At a later phase deposition of lipids takes place in the atheromatous area, and still later there is deposition also of calcium.

The pathologic processes may be linked with the hemodynamics of the coronary circulation. This has certain features which are different in some respects from other arteries of the body. According to Anrep and Segall,[8] the main coronary arteries empty mostly during diastole. During systole the myocardial contraction interferes with their emptying. The intracoronary arterial pressure, stress, and distention are thus greater during systole than in other arteries of the body. This strain and stress are felt mostly in areas where there is greater interference with the free flow of blood, as in bifurcations, branchings, abrupt curves, and points of external attachments, which would explain the greatest concentration of the degenerative changes that occur in those areas. Enos and co-workers believe that eddies develop at the points of branchings and bifurcations during the diastolic recoil of the dilated coronary arteries and are the underlying causes of the early pathologic changes. Moon and Rinehart believe that the initiating mechanism is fragmentation of the internal elastic membrane caused by the intra-arterial tension with secondary degenerative changes induced by this break in continuity of the membrane. Texon[9] believes that changes are caused by a suction effect on the vessel wall due to a decrease in the static pressure of the peripheral stream and corresponding increase in the velocity of the axial stream.

Whatever the exact mechanism or mechanisms may be, there appears to be a definite relationship of the development of the initial lesions of coronary atherosclerosis to the hemodynamics of the coronary circulation. As the process progresses, the hemodynamic changes increase locally because of the progressive impediments to the free flow of blood caused by the increase in the sizes of atheromatous areas.

Besides the mechanical hemodynamic factors, there is also a nerve reflex factor which modifies the flow of blood in the coronary arteries, as shown by Gregg and Shipley.[10] Clinically this is clearly recognized by the marked changes in the circulation under nervous and emotional strain. In these conditions various endocrine factors, notably an increase in secretions of the adrenals, also enter into the picture.

Work as a Factor in Atherogenesis

From the foregoing discussion it will be seen that work may be a potent mechanism in influencing the hemodynamics of the coronary circulation from time to time and may therefore be considered a causative factor in coronary atherosclerosis.

When we speak of work, we must consider all factors associated with work: (1) One factor may be intermittent physical work itself, no matter how light it may be, which may temporarily alter the blood pressure and thus transiently change the circulatory dynamics. This process recurring over many years may have some effect. (2) Another factor may be sedentary nonphysical activity in indoor occupations, with insufficient fresh air and, in some occupations, exhausts and other products of combustion which vitiate the air. Insufficient oxygenation of the blood may thus occur as well as a slowing

of metabolic process due to lack of physical activity which may predispose to degenerative changes. (3) A third factor may be emotional disturbances associated with certain types of work, as well as frustrations, disappointments, reprimands from superiors, and other factors which may affect the nervous system, thereby altering the hemodynamic status of the circulation. (4) A fourth factor may be the monotony associated with some work in this machine age which converts the worker to a mere automaton, taking away his initiative and the power of expression of his talents and converting him to a mere cog in a wheel of a machine. How much this psychologic state acts in the production of somatic changes is hard to tell with our present knowledge of the subject.

These and various other factors associated with work are to be taken into consideration in answering the question as to whether or not work is a competent, producing, ultimate cause of heart disease. To narrow down the question to mere physical work is erroneous. We must consider the human being not as an inanimate machine but as a highly complex organism which may be affected by numerous external and internal environmental factors. Work, which implies earning a livelihood and at its basis is one of the most important factors of self-preservation, involves more elements than mere physical work, which must be taken into consideration. Before a question like the one under consideration can be answered we must clearly know which type of work we are considering, which kind of individual is going to do the work, what are the environmental conditions under which he is working, what are the nerve tensions under which he is to work, and numerous other questions.

We must remember, however, that work is not to be considered the sole cause of degenerative coronary disease. There are undoubtedly a great many other factors in life which are operative, most of which are still unknown. For this reason, as well as for the fact that we have not as yet established the extent of damage any kind of work may produce in the coronary arteries, we are not prepared to answer the question with finality. It is unscientific to claim, however, that work as a cause of any form of heart disease is fiction.

It must be understood that, from a legal viewpoint, chronic pathologic processes that may develop as a result of work over a period of years cannot be considered causally related. There must be a so-called accident which precipitates an acute insult to the heart in order to consider it compensable. In other words, inasmuch as the development of coronary atherosclerosis occurs very slowly and the process cannot be recognized until an acute phase develops, the question may be entirely disregarded from a compensation viewpoint.

Summary

An attempt is made to discuss the question of whether ordinary work over a period of years may cause heart disease. It is pointed out that heart disease, as it is generally considered, cannot be caused by work, but atherosclerosis of the coronary arteries which eventually leads to heart disease may partly be caused by prolonged work over many years. The pathogenesis of the early phases of coronary atherosclerosis appears to be related to the hemodynamic changes in the coronary arteries. These may conceivably be influenced by intermittent alterations caused by work; by nonphysical activity associated with some forms of work; by emotional disturbances accompanying certain occupational pursuits; and by psychologic effects of monotony associated with work at automatic machinery in our modern industrial system.

Inasmuch as the possible effects of work on the pathogenesis of coronary atheromatosis is gradual and there are undoubtedly a great many other factors which contribute to the pathogenesis of the disease, work cannot be considered causally related to the chronic pathologic process from a legal viewpoint. It is the acute phase of coronary disease which enters into the problem of causal relationship.

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Symposium on Employability of the Cardiac

The Heart Association of Erie County is sponsoring a Symposium on Employability of the Cardiac at the Hotel Statler Hilton, Buffalo, New York, March 20, 1959. DR. LOUIS KATZ of Chicago will be the keynote speaker, DR. HERMAN HELLERSTEIN of Cleveland will talk on problems of employment of the cardiac patient, and Mr. FLOYD SMITH of the Workmen's Compensation Board will speak from the labor point of view. Miss ANGELA PARISI, Workmen's Compensation Commissioner, will be the luncheon speaker.

The meeting is open to all practicing physicians, industrial physicians, and personnel representatives who wish to attend.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, this JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Anterior Chest Wall Syndrome

Query: What is the clinical significance of the so-called anterior chest wall syndrome and how do you differentiate it from coronary disease?

Answer: The patient with this syndrome comes in with pain in the left anterior chest. He is apprehensive and scared that he has a coronary attack because he has pain over his heart region. The important thing to demonstrate is that he has no evidence of coronary disease. The diagnosis is confirmed by pressing on his chest wall. Pressure is made first on the normal or right side, never first on the left or abnormal side. Deep palpation over the region of the left costochondral junctions will elicit exquisite pain which will make the patient jump and "hit the ceiling." If the patient is intelligent he will say "Doctor, that is my pain." He will be helped by simple reassurance and will not have to go to the hospital. If he is very frightened he may have T wave changes in the electrocardiogram since fear and anxiety may produce T wave inversions. This is unfortunate because the patient will be considered to have acute coronary insufficiency and may be hospitalized for several weeks. The patient will be a cardiac neurotic for a long time.

Another unfortunate fact is that the anterior chest wall pain syndrome not only is very common but may occur in association with coronary artery disease. Sometimes it occurs a week or two after acute myocardial infarction. Then the attending physician may worry that there has been an extension of the infarction. One way to differentiate the two conditions is by administering prednisone. With a dosage of 5 mg three or four times daily the deep anterior chest pain is relieved in 90 per cent of the cases. The pain may recur after a while, but while the patient is taking the prednisone he feels entirely relieved.

MYRON PRINZMETAL, M.D.

Postinfarction Pericarditis

Query: How do you account for the very low incidence of pericarditis with effusion following myocardial infarction if it is related to the latter?

Answer: It is thought, though not proven as yet, that pericarditis with effusion complicating recent myocardial infarction is caused by sensitization to necrotic muscle tissue. Only a few patients, about 3 or 4 per cent, develop sensitization.

Query: Is there any evidence that postinfarction pericarditis could be embolic in origin?

Answer: To the best of our knowledge, no evidence has been brought forward to show that postinfarction pericarditis is of embolic origin.

Query: Why is the usual post-myocardial friction rub (2nd to 4th day) painless?

Answer: Contrary to prevailing opinion, the usual postmyocardial pericarditis, manifested by an early friction rub, causes pain of the pleuro-pericardial type, which may be very severe. Its true nature is not recognized and the pain is usually attributed to persisting myocardial ischemia, unless the patient is thoroughly questioned as to whether or not the pain is aggravated by deep inspiration or movements of the body.

Query: Is hemorrhagic pericarditis a contraindication for large dose salicylate therapy as well as anticoagulant therapy?

Answer: Anticoagulants are strictly contraindicated in the presence of generalized pericarditis. No ill effect has been observed so far from the use of salicylates.

WILLIAM DRESSLER, M.D.

Book Reviews

The Clinical Physiology of Physical Fitness and Rehabilitation by Ernst Jokl. Thomas, Springfield, Ill., 1958, pp. 194, $6.50.

In this interesting and provocative book the author presents his concepts of rehabilitation. He does not specifically define rehabilitation, but he notes that it has a coordinative role (i.e., coordination of medical, social, psychologic, and vocational and other technics) and a role as a main branch of clinical medicine. The author concerns himself particularly with this latter subject.

The author presents a theoretical basis for rehabilitation which is based on fundamental earlier studies of Conheim, Jackson, Duchenne, Starling, Welch, and Sherrington. He points out that in the past the primary consideration of success of medical therapy has been the amelioration or removal of pathologic processes due largely to the introduction into medicine of nonphysiologic methods (i.e., chemotherapy). In contrast, rehabilitation introduces a physiologic method of therapy and a social criterion of evaluation. The establishment of functional and, ultimately, vocational fitness is now considered the final goal of medical treatment. The author makes the very good point that although the traditional preoccupation of clinical medicine with pathology in its widest sense has thus not been lessened, added responsibilities of a physiologic nature must today be accepted by the physician.

The theoretical concepts which the author evolves are at times difficult to follow, particularly because of the organization of the book with much emphasis on case histories and a lack of a final integrated summary of the author's own concepts. Despite these criticisms, the book clearly emphasizes certain practical and theoretical points of importance in rehabilitation. For example, (1) the importance of physical training (in contrast to physical therapy) in rehabilitation; (2) the fundamental prerequisite for rehabilitation that the underlying pathologic process has been rendered stable before rehabilitation therapy is initiated; (3) the importance of the patient's motivation in rehabilitation; and (4) the difficulty in describing results of rehabilitation in other than human terms.

This book is strongly recommended for all specialists in physical medicine and rehabilitation, and for physicians particularly interested in this field. PHILIP R. LEE, M.D.

Reflexogenic Areas of the Cardiovascular System by C. Heymans and E. Neil. Little, Brown, Boston, 1958, pp. 271, $10.00.

Doctors Heymans and Neil have produced a very complete and excellent review of the different reflex mechanisms of the cardiovascular system, and this book undoubtedly will become another classic to succeed a previous review on almost the same subject written by Drs. Heymans, Bouckaert, and Regniers in 1933.

The monograph begins with a discussion of the anatomy and embryology of different reflexogenic areas. Then it extends into the reflex controls of the circulation, principally by the baroreceptor and chemoreceptor reflexes. However, it does not deal only with these two subjects but also discusses reflexes originating in the lungs and heart, such as reflex pulmonary arterial constriction, the Benzold-Jarisch reflex, the Bainbridge reflex, and volume receptor reflexes.

In addition to a straightforward discussion of the reflexes themselves the relationships of these reflexes to different well-known clinical and physiologic phenomena are also discussed. For instance, the chemical control of respiration is considered in detail; the effects of different drugs on chemoreceptor activity are presented and the operation of reflexes in abnormal states such as in pulmonary embolism, coronary artery disease, and hypovolemia are all considered.

The general tenor of the book is highly scientific, and almost all *important* studies ever performed on cardiovascular reflexes are reviewed in detail. However, the style of writing is light

enough so that one not well versed in the field of circulatory reflex physiology will still have no difficulty in reading the book. The easy style has not in any way detracted from the scientific quality of the work.

Study of this monograph should be considered an absolute necessity by all persons interested in cardiovascular research. Though all physiologists might not agree with the extreme degree of importance placed by Heymans and Neil on some of the reflexes, nevertheless, the completeness of the review will in itself be of great value to all readers. Also, clinicians who wish to know the difference between truth and fantasy in relation to the many reflexes that have been invoked to explain disease conditions will find this book to be a fertile field of precise information.

ARTHUR C. GUYTON, M.D.

Fundamentals in Cardiology by John B. Wild. Thomas, Springfield, Ill., 1958, pp. 83, $4.50.

This little volume attempts to cover the hemodynamic changes occurring during systole and diastole in the normal heart, in valvular disease, and in atrial and ventricular septal defects. It is evidently based on experiences of cardiac catheterization. As such, the volume hardly deserves the title, "Fundamentals in Cardiology." It covers relatively few of the fundamentals one has to bear in mind in the study of the normal and of the diseased states of the heart and circulation, and these few are too briefly described. One would like to find, for instance, actual numerical figures of the normal variations of the intraatrial and intraventricular pressure changes in different individuals during systole and diastole and the maximum and minimum variations in different degrees of the pathologic states the author touches on. A discussion of the mechanism of production of the first heart sound would be worthwhile rather than the mere mention of its mitral and tricuspid valve components. If he had to state that the T wave in the electrocardiogram is inverted in ventricular hypertrophy, he should have specified in which leads this occurs. One would also like to find descriptions of the hemodynamic changes in patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, and in other congenital defects of the heart and basal vessels. The material he does cover is at times not clearly described.

The book should be of help, however, in calling the attention of the student and practitioner to the need of visualizing the hemodynamics occurring in the heart. He is right in his introductory statement that "to them (the medical student and, he should have added, the practicing physician) the 'a,' 'c,' and 'v' waves are something that happened in physiology." LOUIS H. SIGLER, M.D.

The Lipoproteins: Methods and Clinical Significance by F. Homburger and P. Bernfeld. S. Karger, New York, 1958, pp. 94, $4.00.

This symposium is the third of a series devoted to the subject of research advances applied to medical practice.

It consists of eight short articles, each contributed by an author or group of authors whose own investigations in the field of lipoproteins are well known. The first two chapters deal with a description and history of the lipoproteins. They are written by Drs. George Mann and J. L. Oncley, respectively, and present a good review of the subject. This is especially true of the chapter contributed by Dr. Oncley, a pioneer in lipoprotein research.

Dr. Bernfeld, one of the symposium's coeditors, contributes a purely technical discussion of a new method for the determination of beta-lipoglobulin. Lipoprotein lipase is discussed by Dr. Joseph Bragdon especially in relation to its possible uses in clinical medicine.

The remaining four chapters will be of special interest to the practicing physician. The most voluminous of these is a discussion by Dr. John Gofman of his work on the clinical significance of low density serum lipoproteins as determined by ultra-centrifugation. Whether one agrees or disagrees with Dr. Gofman regarding the usefulness of these determinations to the clinician, his chapter is an excellent presentation of most of the important parts of his work to date.

The contribution of Dr. Martin Hanig relates

to his experiments with lipoproteins extracted from normal and atheromatous aortas, and the possibility of finding the abnormal fractions in the blood of patients with coronary atherosclerosis.

The two final chapters, one by Dr. Mary L. Petermann and associates on lipoproteins in women with carcinoma of the breast, and the other by Dr. Jessie Marmorston and associates on steroid hormone excretion after myocardial infarction, are of particular interest because of the clearly shown relationship between the sex of the individual and the type of lipoprotein in the serum, both in health and disease. In addition, Dr. Petermann's chapter touches on a field which will certainly become of increasing importance; namely, the relationship of lipoproteins to the malignant state.

Most authorities on lipid metabolism feel that the usefulness of lipoprotein determination to the practicing physician is limited not only by the expense of the procedure, but also by the fact that as much, if not more, information relative to coronary atherosclerosis can be gleaned from a simple determination of the serum cholesterol. Those who so believe would thus conclude that research advances in the lipoprotein field have not yet produced technics applicable to clinical practice to any degree. It could therefore be argued that this symposium serves no purpose, at least as far as satisfying the stated objective of the series and, therefore, has little reason to be published from this standpoint.

Nevertheless, determination of the lipoproteins will certainly become more widespread in the future, and a symposium of this type provides an interim report in a field which will eventually provide technics that will be clinically applicable to a much greater degree than at present. As Dr. Mann states in the first chapter of the book: "The area of lipoprotein research is charged with controversy. Few fields of science contain such a diversity of conclusions reached from a single body of data. This heat and contention, while sometimes unpleasant and diversionary, may yet be useful because it spurs the search for new data."

The book will be of value to all those interested in the field of lipids and lipoprotein metabolism, particularly with regard to the relationship between these components of the human serum and the development of coronary atherosclerosis and other diseases.

LOUIS E. SCHAFFER, M.D.

A Manual on Cardiac Resuscitation, ed. 2, by Robert M. Hosler. Thomas, Springfield, Ill., 1958, pp. 208, $4.00.

This manual on cardiac resuscitation is a revised and enlarged edition of an earlier work on the same subject. In no sense does this work claim to be any more than a handbook to present the practical methods for combating a terrifying emergency which can confront the physician, the surgeon, or the anesthetist. It is in no sense an exhaustive treatise on the subject. The book is exceptionally well organized and contains a number of practical summary tables that can be very useful to anyone using the work for teaching.

One of the most interesting features is a discussion of the course in Cardiac Resuscitation given by Dr. Hosler *et al.* and the follow-up case reports of those taking this course. There is no doubt that any physician could benefit by having this volume at hand for study and research because it concerns a subject which has received, up until lately, not nearly the amount of attention that it deserves.

LOUIS F. BISHOP, M.D.

Advances in Electrocardiography, edited by Charles E. Kossmann. Grune & Stratton, New York, 1958, pp. 280, $9.75.

This book consists of a series of lectures given by members of the staff of New York University. It is divided into four parts:

Part I: The source of the electrical potential of the heart is described in terms of the transmembrane action potential produced by the excess of ionic flux of sodium into the cell.

Part II: Problems arising in relation to the conducting medium surrounding the heart are described. Among the subjects covered are the concept of image space, lead vectors, Burger's triangle, and the lead field concept of McFee and Johnston. Problems of vectorcardiography are

reviewed, and a variety of orthogonalized and normalized lead systems are described, as well as the concept of the universal vectorcardiograph and the differential vectorcardiograph.

Part III: The normal and abnormal spread of the excitation through the heart and the recovery of heart muscle are described. In a chapter on congenital heart disease, Brumlik points out: "the cardiac malformation itself affects the electrocardiogram only in rare instances. It is the effects of the anomaly: hypertrophy, dilatation, atrophy, block, ischemia which usually produce the electrocardiographic abnormalities. Since certain malformations have a tendency to provoke a certain type of response in the heart, a corresponding alteration in the electrocardiogram can be expected and is often found. Exceptions are so numerous, however, that a precise diagnosis of a congenital cardiopathy can only be made by evaluating the electrocardiogram in the light of results of other diagnostic procedures."

Part IV describes recent experimental work on abnormal cardiac rhythms. An interesting observation is that upright P waves in leads 2 and 3 can occur in A–V nodal rhythm. This can occur if the stimulus spreads from the A–V node upward through the A–V septum and then downward through the free walls of the atria.

The advanced student of electrocardiography will find the book interesting.

EMANUEL GOLDBERGER, M.D.

Atlas and Kurzgefasstes Lehrbuch der Phonocardiographie by K. Holldack and D. Wolf. Georg Thieme Verlag, Stuttgart, 1958, pp. 179, D. M. 49.50.

This is both an atlas and a concise textbook of phonocardiography. It first describes the physical foundations, technic, and apparatus of phonocardiography. This is followed by a practical introduction to arterial and venous pulse tracings as well as tracings obtained by way of the esophagus. Chapters on normal and abnormal phonocardiographic patterns follow, with a well-documented chapter on the phonocardiogram in congenital heart disease. There is an extensive bibliography with references to both recent German and American literature.

The book is recommended to those with a working knowledge of German.

EMANUEL GOLDBERGER, M.D.

Basic Cardiology by T. R. Gumpert. John Wright and Sons Ltd., Bristol, England, 1957, pp. 168, $6.00.

This small volume covers a series of lectures the author has given to medical students and to postgraduates. It is a synopsis of available knowledge of cardiology, well systematized and skillfully presented. The author necessarily has eliminated more comprehensive descriptions found in usual textbooks on cardiology and most illustrative material essential for a thorough understanding of the subject. He falls short particularly on therapy, and some of his therapeutic procedures are open to question. Thus, the dosage of penicillin he advocates in subacute bacterial endocarditis is inadequate. He mentions some antihypertensive drugs in the treatment of essential hypertension but does not describe their dosages and methods of administration. He advocates the use of a chocolate-covered tablet of nitroglycerin for angina pectoris, which is certainly not the usual method of administration of this drug. He mentions little of other drugs and methods used in the treatment of this condition. He prefers the use of phenylindanedione (Diudevan) as an anticoagulant in myocardial infarction rather than Dicumarol and Tromexan because it is less toxic and is an oral preparation, forgetting that Dicumarol and Tromexan are also given orally. He does not describe the methods employed in anticoagulant therapy and its control by prothrombin-time determinations. The treatment of heart block is incomplete.

Some other statements made are questionable. For example, the electrocardiogram in Figure 30, which he interprets as partial 3:1 heart block, may be considered to be complete heart block and left bundle branch block. Figure 62 does not seem to fit in with its legend. He states that the electrocardiographic changes of acute cor pulmonale resemble those of myocardial infarction but does not point out the differences.

These and some other shortcomings do not deprive the book of its good qualities. The author has carefully selected his up-to-date ma-

terial and presented it in a delightful and easily readable manner. It is highly recommended as a short and efficient review of the subject of cardiology.

LOUIS H. SIGLER, M.D.

Clinical Electrocardiography by Manuel Gardberg, with chapters by R. Ashman, L. Rosen, and L. Levy. Hoeber, New York, 1957, pp. 326, $12.75.

In this book the basic subjects of electrocardiography are presented with a clear point of view. In a simple and objective manner Dr. Gardberg explains the complicated problems of the electrical phenomena of the heart and includes good schematic figures to illustrate them in a practical manner. Very careful work must have been carried out by the author in order to develop the vectorial analysis of the ECG curves, the schema of the solid angle, and other problems that not everybody is able and willing to analyze.

Using the solid angle, the author explains the genesis of the morphology of precordial leads in accordance with the position of the heart. His explanation of the activation of the heart is good, even though it is presented very schematically, omitting some aspects such as atrial activation. His point of view of the ventricular activation in normal conditions and in the presence of bundle branch block and its relation to the VCG curves is excellent; he does not emphasize, however, the importance of septal depolarization and the sequence of this process—from the middle of the left septal surface toward the basal portions. He does not discuss the functional separation of the septal masses as has been demonstrated at the Instituto Nacional de Cardiología of Mexico and recently confirmed in the Japanese literature.

The ventricular gradient, a subject in which Dr. Gardberg excels, is magnificently treated in this book, and we wish to emphasize the importance of this difficult subject, so simply and clearly explained by the author.

The chapters on ischemia and injury are very good and are complemented with an additional article on coronary insufficiency. A wide analysis of the sequence of electrocardiograms in coronary insufficiency syndromes is also presented in this chapter. The ventricular gradient is applied in a practical manner. We should have liked a greater number of electrocardiograms to illustrate the above subjects.

Bundle branch blocks are superficially treated, omitting again the importance of the septal barrier in the genesis of bundle branch block morphologies. Although there are some electrocardiograms with rSR or qR morphologies in lead V_1, the diagnosis of incomplete right bundle branch block is not considered. The possibility of right auricular hypertrophy in the presence of qR morphologies in V_1 is disregarded.

The chapters on rhythm disorders and metabolic or electrolytic disturbances are well treated and widely explained with sufficient illustrations.

In summary, the book is excellent, it has an abundance of scientific information, and is well presented. Mostly, the author is in agreement with our own general criteria; therefore, we have little criticism to make. We recommend this treatise as worthy of a special place in every library devoted to this subject.

DEMETRIO SODI-PALLARES, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

The Care of the Geriatric Patient, edited by E. V. Cowdry. C. V. Mosby, St. Louis, 1958, pp. 438, $8.00.

Electrocardiography by Michael Bernreiter, Lippincott, Philadelphia, 1958, pp. 133, $5.00.

De Circulatione Sanguinis by William Harvey (trans. by Kenneth Franklin). Charles C Thomas, Springfield, Ill., 1958, pp. 184, $4.50.

Difficult Diagnosis: A Guide to the Interpretation of Obscure Illness by J. H. Roberts. W. B. Saunders, Philadelphia, 1958, pp. 913, $19.00.

Cardiovascular Sound in Health and Disease by Victor A. McKusick. Williams & Wilkins, Baltimore, 1958, pp. 570, $15.00.

The Chemical Prevention of Cardiac Necroses by Hans Selye. Ronald Press, New York, 1958, pp. 235, $7.50.

Cardiac Arrest and Resuscitation by Hugh E. Stephenson, Jr. C. V. Mosby, St. Louis, 1958, pp. 378, $12.00.

Nutrition and Atherosclerosis by Louis N. Katz, Jeremiah Stamler, and Ruth Pick. Lea & Febiger, Philadelphia, 1958, pp. 146, $5.00.

College News

1959 Annual Meeting

The Eighth Annual Meeting of the American College of Cardiology will be held on May 25–29, 1959 inclusive at the Benjamin Franklin Hotel, Philadelphia. Dr. Robert P. Glover has been appointed Local Convention Chairman.

Call for Abstracts of Papers

All members of the College are requested to submit or urge their associates to submit 250 word abstracts of original scientific studies in the field of cardiovascular diseases for the Annual Meeting of the College in Philadelphia on May 25–29, 1959. These abstracts are to be mailed to the Chairman of the Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y., for consideration by the Program Committee.

Eight papers will be selected for presentation by members of the College at the Annual Meeting. Abstracts must be submitted by February 15, 1959. Your cooperation is essential to our having a good meeting.

Scientific Exhibits

Space is still available for presentation of scientific exhibits on any aspect of cardiovascular diseases. Those who wish to present an exhibit should send a description of the exhibit to Seymour Fiske, M.D., Chairman of the Arrangements Committee, 150 E. 71st St., New York, N. Y.

The Clinical Workshops

In 1955 the American College of Cardiology inaugurated an original form of exchange of medical "know-how"—The Clinical Workshops. As a result of many requests the workshops will be reactivated during 1959–60.

The preceptors to be invited will, in the main, be selected from the ranks of the Fellows of our College, who in the past have freely given of their time and knowledge. Their efforts will make it possible to provide workshops, in which clinical and procedural "know-how" will be stressed. Offers from preceptors for consideration will be appreciated by the Committee.

Requests for special workshops will be given every possible consideration. Applications should be addressed to the chairman of the Clinical Workshop Committee.

The Clinical Workshop program and a contemplated series of postgraduate courses constitute the formal professional education activities of the College. Further announcements will appear in the Journal.

JOSEPH B. WOLFFE, M.D., *Chairman*
Clinical Workshop Committee, A.C.C.
Fairview Village, Pa.

Trustees Appoint Executive Director

In order to place the office of the College on a firm basis of continuous management, the Trustees have created the post of Executive Director. The first appointee to this new office is our founding Secretary, Dr. Philip Reichert, who will hold the post for a period of four years. This will give ample time for finding and training a possible successor upon Dr. Reichert's retirement.

To effect a smooth transition to the new position, Dr. Reichert has relinquished his elected post as of January 1, 1959, the Assistant Secretary and Assistant Treasurer moving up to the full titles. Dr. Henry Russek becomes Secretary of the College and Dr. Louis F. Bishop becomes Treasurer.

Certificate for Associate Fellowship Abolished

At the 84th Meeting the Board of Trustees in New Orleans abolished the certificate for Associate Fellowship as of the date of that meeting. An Associate Fellow may apply for advancement in grade two years after his induction into the College. There have been a few changes in the rules for basic eligibility: inquiry to the office of the Executive Director in the Empire State Building will bring full details that will apply to a particular case.